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SOME CLINICAL ASPECTS OF LACTATION*

BY

HAROLD WALLER

This lecture is in memory of a great paediatrician who stood high in the regard of his colleagues and by his teaching and writing did much to encourage the study of children's medicine by general practitioners. Still's book on the common disorders of health in childhood must have stirred an impulse in many of us, and to read it was a lesson in his habit of patient clinical observation and methodical record from which we could hardly fail to profit. From my knowledge of him he would have been too courteous to express surprise at your choice of lecturer, but I am encouraged to think he would have approved your selection of subject for its bearing on the preventive side of medicine. And I believe I may add that this sign of your interest in breast feeding will be an encouragement to the large number of doctors who, like myself, spend much of their time working for maternal and child welfare.

I have heard this work described as a treadmill, but I protest I have not found it so. Its problems are various and complex, not unlike those which occupy the field naturalist. As a branch of medicine it has not lost for me the attraction it has held ever since I first saw it practised by Eric Pritchard, and I still recall the thrill of its early promise at a time when the rate of infant mortality was nearly three times as high as it stands to-day. I doubt whether even now its possibilities have been fully grasped, and I have sometimes thought its financial support by the Government was made prematurely; for certainly its direction by public health officials so early in its development seems to have had the effect of slowing progress and cramping individual enterprise in breaking new ground, and to have had the tendency to call a halt at a stage which was merely easy to administer. Outstanding among its problems is the unreliability of lactation, challenging us daily to find its solution; for it is at the infant welfare clinic, more clearly than anywhere else, that the contrast in growth between the naturally and the artificially fed infant is apparent. There we see the effects of artificial feeding, not as you would prescribe it, not always as we ourselves prescribe it, but too often as it is used in the most haphazard manner on the direction of a relative, the recommendation of a neighbour, or the instructions of the manufacturer. Frequently also we see it adopted hastily because of some symptom which a mother's anxiety has attributed to breast feeding. Working against such influences as these, any attempt to study the causes of lactation's failure is difficult enough, but hitherto it has also meant groping about with little help from physiology or for that matter, from anatomy or pathology, and in consequence with no more success than could have been expected. In a large proportion of the women who bring their babies to us, breast feeding has already failed or has declined beyond the point at which its revival is practicable with the means at our disposal. So many of these failures occur within the first weeks that it is with them I shall be concerned here; not only because of the special risk of artificial feeding in the early weeks of life but because, of all the various aspects of this work for infant welfare, this is the most obstinately resistant to improvement. Moreover, besides the risk to babies, it involves something which I hold is too lightly regarded; the very real and lasting regret which the failure to breast feed brings to many women. And lastly, owing to special conditions which surround the start of lactation, women are at this stage involved in the risk of mastitis and breast abscess, a complication which certainly is far too lightly regarded and is often most indifferently treated.

And so it has come to pass that the necessity to save infant life has been the mother of more and more ingenious invention, and with the aid of the ancillary sciences of chemistry and bacteriology, not to mention the spur of commercial enterprise, artificial feeding has been transformed from a dangerous gamble into something approaching a successful makeshift for human milk. Meanwhile there has, of course, been no reluctance to speculate on the causes of the frequent failure of breast feeding, and a number of explanations has been evolved; some of them of a somewhat facile type which have come to be accepted almost uncritically. Such, for example, is the view that the function of lactation has suffered a decline in conditions of modern civilization. Even more commonly, perhaps, is it held that women have developed a

* The George Frederick Still Memorial Lecture, delivered at the Annual Meeting of the British Paediatric Association, Windermere, on April 26th, 1947.

widespread unwillingness to undertake the task. Both views may well contain elements of truth, indeed I suspect they do; but they are at present valueless since they have never to my knowledge been investigated in such a way as would establish their truth or falsity. They remain in the category of what have been so aptly called 'hieratic pronouncements which rise superior to the need of proof.' Certainly lactation ceases prematurely in a high proportion of women, and the plain truth is that of many we cannot say with any certainty what is the cause. There is not a textbook of obstetrics or paediatrics but pays tribute to the superiority of natural feeding, while mass statistics showing the higher death and morbidity rates of the artificially fed have been compiled again and again in many countries. The remarkable fact about this situation is that, whereas the effort towards increasing the safety of artificial methods has been unremitting, enquiry into the causes of failure to breast feed has scarcely been seriously attempted.

Milking of Animals

But there is something even stranger here. The very discovery that the milk of an animal can be purloined and used for the service of mankind has depended upon mastery of the difficulty we are considering. It postulates that the first exploiters of artificial milking must, wittingly or unwittingly, have complied with certain fundamental principles governing milk secretion; an example of experimental physiology, made we know not how long ago, whose success would surely command more of our respect were it not so familiar. Those who recall Karl Pearson's learned reconstruction of the 'Mother Age' and the wealth of evidence he marshalled of its impress on language, folklore, and culture, will find it easy to believe this discovery was made by women; and I have wondered whether one of its earliest purposes may have been to shorten the period of breast feeding which must have extended to years rather than months. From what we know of the results of feeding raw and unclean milk to very young babies, it can seldom have brought salvation to the newborn, a fact which possibly accounts for the heroic place in myth and legend of the occasional survivors such as Romulus and Remus. But this is too wide a digression. We need to remember that, after many thousands of years of domestication and selective breeding, dairy farming today retains but a trace of the difficulty of persuading an animal to allow herself to be milked, which must have faced the early experimenters. As late as the Greeks a frieze depicts the device of tying the calf to the horns of its affronted plunging mother. The submissive animal we know today may still need to be calmed, but it is probably enough to place food in the manger at milking time. The lore of milking has its place in literature from Homer onwards, and to take a recent example it is described in Hardy's *Tess of the D'Urbervilles* with all an expert's knowledge; how an animal will 'let down' her milk freely to one and withhold it from another; the need for the milker's hands to work with speed and gentleness; the inhibiting effect of pain or fright. There is a passage in which the men discuss the cause of a morning's unsuccessful milking which one attributes to disturbance of the herd by the arrival of a new farm hand, and the dairyman agrees that may account for it. There is the knowledge that the last milk to be withdrawn is richer in cream than the rest and, above all, the importance of complete emptying of the udder if the yield is not to decline and even to cease altogether. For this reason the dairyman reserves to himself the 'hard yielders,' for there are marked differences among animals in the ease with which the milk can be withdrawn. These facts are the common knowledge of the stock keeper, and have enabled him to maintain lactation in animals for many months and often at an abnormally high level.

The Mechanism of 'Letting Down'

Now the mechanism of 'letting down' has been the subject of much patient research by agricultural physiologists and insight into it was gained when Tgetgel (1936) showed it coincided with a sudden rise of intramammary pressure. This produces a downward movement of the gland's contents, forcing them into the larger ducts and their reservoirs or 'cisterns' with sufficient strength to open a kind of rudimentary valve situated at the base of each teat. Hammond, of the Cambridge School of Agriculture, holds that between milkings the most fat-laden fraction of the milk is delayed by capillary attraction in the lumina of the finest tubules and that some form of expulsive force is essential to dislodge it; the greater volume of what is secreted meanwhile drains down into the more capacious part of the duct system. This explains why milk obtained from the cisterns by catheter is all low in fat content, whereas when obtained with the aid of the expelling mechanism the fat content rises as milking proceeds. Again, if the four quarters are milked in turn this difference in the fat content of fore and hind milk is present in milk from the first quarter but diminishes progressively in the others. By the time the last quarter is milked it has disappeared, for by then the fat has become evenly diffused throughout the contents of the cistern.

It has been shown by Ely and Petersen (1941) that the rise of intramammary pressure can be greatly reinforced by the subcutaneous injection of pitocin; thus if the usual yield at milking is 16 lb., it can by this means be increased to 21 lb., and the fat content of the extra volume is as high as 17 per cent. This effect is obtained after the udder is completely separated from its nerve supply, and suggests that the action of the posterior pituitary is upon plain muscle around the alveoli and in the walls of the duct system. These investigators have also shown that the inhibition of the 'letting down'

mechanism caused by fright can be reproduced by injecting adrenaline into the blood stream, and that both types of interference can be overcome by pitocin. The mechanism, which normally is reflexly evoked by stimulation of the teats, requires that a certain degree of milk tension within the udder shall have been reached; that is to say, a certain volume of milk must have accumulated there. If milking is attempted before this it will not succeed, for the milk will not be let down.

Outside the laboratory, and in conditions less artificial than those of the milking shed, there are opportunities to watch this mechanism in action; it is, for example, easy to observe in sheep grazing with their young lambs beside them, though it is not quite easy to keep close watch on more than a few at a time. In a group of five observed for a matter of two hours I found that the lambs, which were a little over three weeks old, sought their mothers for milk on an average every three and a half minutes. When the search is successful the lamb reveals it quite unmistakably by a vigorous wriggling of its tail which lasts rather more than a minute, and by means of this signal I found they were rewarded with milk at every sixth attempt, on average, or almost exactly three times in the hour. Now it was only at these times that the sheep would stand still and allow the business of grazing to be interrupted for suckling; at all others they countered the young's demands by moving forward and cropping the grass. On the other hand it sometimes happened that the lambs appeared to be late in applying at the appropriate interval and the sheep would then stop feeding and look around. It was evident the lambs had learned this was an invitation to feed for they rushed up at once and were always rewarded. To me it seemed the mothers were sensitive to the level of milk tension and perhaps experienced relief when the udder was drained. The udders of all these animals were small, but in districts where sheep's milk is used for making cheese and is withdrawn twice daily they become stretched to an enormous size. This is by virtue of the elasticity of both the duct system and the tissues which compose the gland's covering. From prehistoric times the dairy farmer has learned to take advantage of this property of the udder whereby normally the secreting cells are guarded from damaging compression by undue distension of the alveoli with milk. To obtain the largest yield he will, if he is wise, lengthen the intervals between milkings gradually so that the stretching can adapt itself to greater and greater volumes of milk. Too long an interval imposed suddenly at the start of the first lactation results in high milk tension and causes pain, and the yield declines and may cease within a short time.

I have reviewed these facts, many of which must be well known to you, since when taken together they allow us to define certain requirements which, it appears, must be met if the mammary gland is to fulfil its function. It is known that milk secretion is continuous and we have seen the demands of the young are intermittent, and the mother must feed herself. For these reasons, and because leakage from a gland opening on the surface of the body means wastage, some capacity for storage is necessary. If the activity of the secretory cells is not to be hindered, this storage must be provided in the duct system; and, finally, when its limit has been reached milk must be removed. The gland's power of expulsion is not of itself great enough to do this and must be aided by withdrawal, a combination which is guaranteed by the recurring hunger of the young animal and the fact that stimulation of the teats reflexly evokes a rise of pressure within the gland. We know from artificial milking that this contribution from without is provided by compressing and emptying the terminal milk reservoirs; presumably the young obtains its food by the same means. (If a simile is permissible, this action is more akin to the principle of the Higginson syringe than to that of the suction pump.) It is worth noting that in natural conditions there would seem to be little likelihood of the gland becoming overloaded, for in the example of the lambs their demands for food were far more frequent than could be met. Five out of six were rejected by the mother and it is she, guided by her own sensations, who decides when the time for a release of milk has been reached. So much for a very fragmentary survey of facts revealed by comparative studies. Is there anything to be learned from them that can be applied to human affairs ?

The Human Mechanism

Certain resemblances are clear enough. Most women, though not quite all, are fully aware of the expulsive reflex which they call the ' draught ' and say it ' comes in ' as the baby draws the nipple into its mouth or a moment or two afterwards. It is usually described as a ' drawing feeling ' or as the tingling of ' pins and needles ' and is felt in both breasts simultaneously, at which moment the child can be seen and heard to start drinking. The flow may come faster than the child can swallow, so that it may have to stop feeding if it is not to choke. If it draws away from the breast the milk can sometimes be seen spurting to a considerable distance beyond the nipple, but as a rule this is confined to the early weeks of lactation; later, when the duct system has become stretched, it is able to retain the milk without its overflowing. I have asked many women how long the draught lasts, and while they all say the sensation is quite brief they can seldom be more definite. From some who have tried to time it, it would appear to last between 30 and 45 seconds; ' though,' as one put it, ' it seems to help the milk to flow for much longer than that.' This may well be the elastic recoil of the distended ducts. Generally it is hard to obtain any clear or detailed description of the draught, which I take to be due to the well-known difficulty of describing

visceral sensations. When feeding goes smoothly and the baby habitually sleeps for a space of some hours, the draught becomes conditioned to the interval and may be so punctual that it anticipates the act of suckling should the baby sleep beyond the usual time. When this happens many women realize it is wise to rouse it and are glad of the relief which emptying the breasts brings, a fact that recalls what I* said about the unpunctual lambs. The child feeds contentedly, and fractional test weighing shows it feeds rapidly; of this I have many records, such as 8 oz. taken in the space of three minutes. In my view any harm which results from babies taking large feeds in a short time has been much exaggerated. Many give up as soon as the flow wanes, and will only resume if put to the other breast. So, too, if for any reason the draught does not immediately come to its aid, the baby may give vent to a storm of protest, and I see this at my clinics from time to time if a woman is embarrassed by a request to feed her child so that I may watch some point in her method. If she can be calmed and the inhibition be removed, the feed goes smoothly enough. All my experience goes to prove that women in general are aware of the importance of the draught, and of the assistance it gives the child, indeed that without its aid the child can obtain little. They realize that its punctual recurrence means the breasts fill regularly and the yield is being maintained; and, conversely, if its strength declines and its arrival is irregular, production is waning. This, of course, is reflected in the child's behaviour.

It has long been known that the difference in fat content of the first and last milk to be withdrawn corresponds with what has been found in animals, and the difference which I mentioned can be demonstrated when the four quarters of the udder are milked in turn applies to milk from the two breasts. By the time the first breast has been drained the same diffusion of fat has taken place throughout the milk in the second, and fore and hind milk have approximately the same fat content (Waller, 1943). When investigating this point some years ago, I found that after the breasts had been fully drained a further flow could readily be obtained by injecting pituitrin, and this extra yield had a fat content as high as 11 and 13 per cent. We can, I believe, assume that the draught and the letting-down mechanism are not only identical but are essential for effective drainage of the mammary gland.

If this view is correct, then it becomes a fact of much significance that in many primiparae any aid from the expulsive mechanism is difficult to detect during the first fortnight after delivery; indeed it is often conspicuously lacking. The account just given scarcely applies to the initial phase of the first lactation but is rather a description of its action from about the fourth week onwards. I have discussed the characteristics of the early days in some detail in a paper published recently in this Journal (Waller, 1946), giving reasons for believing it is a period when drainage of the breasts is commonly incomplete, with the risk this always involves of reversionary changes. Yet adequate emptying at this stage is, I believe, so essential to the ultimate success of breast feeding that I will summarize as briefly as possible the difficulties which arise, as well as certain methods of dealing with them.

Difficulties of Breast Feeding

There are two factors, particularly in the first lactation, responsible for a high degree of milk tension occurring at this time. The start of milk secretion may be sudden and the volume produced so great that it cannot be accommodated by the duct system, as yet unstretched. Together with this the skin covering the breasts may be thick and unyielding, and in consequence the breasts become rapidly swollen, heavy, and oedematous, and the outflow of milk is then hampered and sometimes entirely obstructed. For various reasons the newborn may be unable to make any effective contribution to emptying the breasts; it may, for example, take several days to recover from the effects of labour, or it may be premature, or weakly from other causes. Even the drowsiness and lethargy of the ordinary icterus neonatorum may be enough almost to extinguish its desire to feed for two or three days. Then developmental defects of the nipples are extremely common, and in a high proportion appear to be associated with poor development of the lacteal sinuses. The nipple that cannot easily be drawn far back into the baby's mouth is liable to get damaged and this is a source of great pain to the mother, and often of apprehension as well; while the combination of injury and incomplete drainage is a very fruitful source of infection.

Management of Feeding

Together these make a formidable list of which any one is capable of frustrating breast feeding at its outset, and in the article to which I am referring I told how, at the hospital at which I work, we have tried to overcome them. This includes the systematic examination of all patients for structural defects of the nipples early in pregnancy and the use of a simple orthopaedic appliance, which has proved effective in all but those which are grossly deformed. We teach the manual expression of colostrum to all primigravidae and ask them to practice it daily during the last six weeks of pregnancy. The subsequent outflow of milk during the first days of lactation is so much more free that we believe it dilates the duct system and enables a primipara to start with something of the advantage possessed by a woman who has already breast fed a baby. When the start of secretion is sudden and threatens to produce engorgement it is controlled by using the synthetic oestrogens. Lastly, we set great store by the manual removal of milk to ensure adequate drainage which at this stage we do not expect the baby to be able to accomplish. The

women learn how to do this themselves and with a little supervision at first become exceedingly skilled at it.

From this combination of measures the most important fact to emerge is that the reflex expelling mechanism is usually well in evidence before the mothers leave hospital on the twelfth or thirteenth day, and the primiparae can by then recognize the draught, if not as clearly and regularly as the multiparae, nevertheless quite distinctly. Moreover it is evident that milk is expelled, not only by the freedom with which it flows from one breast as the child feeds at the other, but by the fact that the child obtains it much faster, and that the amounts taken at each feed become approximately equal, with a tendency to rise steadily day by day.

Management on these lines demands a delicate appreciation of what constitutes excessive milk tension; and, since it cannot be measured as blood pressure can be measured, it can only be gained by clinical experience. In this the nursing staff at my hospital have attained a very high degree of efficiency and they keep a close watch on each woman, not only from day to day but several times during each of the first six or seven days. Even so, when going round the wards I can often tell from the first half-dozen patients that there has been a rush of admissions and the staff has been overworked. The size of the babies' feeds then shows too great variations and they have had to be complemented too often by milk expressed by hand. The charts record the oestrogen preparations have been used more than is usual. There may be two or three mothers with injury to the nipples, and suckling has had to be withheld for forty-eight or seventy-two hours to allow healing. I shall be asked to advise certain women to stay longer than they had expected in order to ensure that feeding is secure. I emphasize this because it serves to show how delicate are the points of nursing technique during these early days if the secretory needs of the breast are to be met so that production will be maintained. If half a dozen patients are delivered within a few hours of each other they will all simultaneously reach the stage when, for reasons I have mentioned, the risk of engorgement arises; and this may coincide with the arrival in the wards of a group of new pupil nurses. This is the nature of maternity work in present circumstances. On another day the records will be quite different, for the staff have been able to give the necessary watchfulness to each patient, to anticipate in whom difficulty was likely to arise, and to circumvent such difficulty successfully.

There is nothing particularly difficult in establishing such a regime; nothing more, shall we say, than training a staff in the detail of routine to achieve asepsis in the operating theatre. The underlying principles must be understood by the whole team, and the technique learned by every member; its detailed observance must become a matter of conscience. Perhaps I should have put first the necessity to renounce the view that breast feeding is a simple physiological function which needs for its success nothing more than a woman's willingness, and accept the fact that this only holds good for about a quarter of our primiparous women, and that some degree of preparation and skilled help is needed for the rest. I attach great importance to this attitude because I feel sure the tendency to attribute failure to unwillingness often serves as an evasion of problems for which the solution can be found. Certainly it is our experience that, if the start of breast feeding can be made easy and painless, and the woman saved anxiety about her capacity to succeed and given the assurance that her baby is thriving, she will not lightly give up. It is also essential to get acceptance by everyone in the maternity hospital that their responsibility extends beyond the short period of the puerperium, and that in the matter of infant feeding the aim is not merely to see that by one means or another the baby receives the necessary quota of milk, but that the mother's lactation is so managed that it is secure. Like most hospitals we return some 85 per cent. of women 'wholly' breast feeding when they leave our wards; but we have learned that there must be many reservations before this figure can be taken as synonymous with 'securely' breast feeding. The soundness of methods employed during the lying-in period cannot be assessed at fourteen days; it must be tested by results at intervals such as three and six months. Thus, in an experiment which I have described elsewhere, we found that, out of a hundred primiparae who had been taught the daily removal of colostrum, eighty-three were successfully feeding at six months compared with but forty-two of a similar number of controls, the management of the two groups after delivery having been identical. We were at the time concerned to test the value of the pre-natal exercise and were highly gratified with the result. On reflection, however, it was chastening to realize how unsatisfactory was the performance of the controls; for of these we had recorded eighty-three as 'wholly' breast feeding when they left the hospital in the belief that we were duly on guard against the fallacies latent in that deceptive term. The discovery served to drive home once more how dependent the maintenance of milk production is upon the prompt establishment of free drainage, and pre-natal tuition has since become the rule for all primigravidae and those who have failed in a previous attempt to breast feed. A recent review of three hundred primiparae who passed consecutively through the wards showed that 237, or 79 per cent., were still yielding their babies at six months all the milk they needed.

Duties of the Paediatrician in Relation to Feeding

Is our customary advocacy of the advantages of breast feeding sufficiently sincere to see that the rather meticulous detail I have described shall be forthcoming? and, if so, shall we demand it of

the obstetricians or undertake it ourselves? You will have guessed that I favour making it the responsibility of the paediatricians, and for this reason: though there are outstanding exceptions, I believe it true to say that to most obstetricians the supervision of infant feeding comes as an anti-climax to all the problems and anxieties involved in safeguarding women through pregnancy and labour. The majority are very content to leave the care of the infant to the nursing staff. I recall an animated discussion on this subject many years ago, during which an eminent obstetrician confessed that he asked to be relieved of all responsibility for the newborn once the cord was tied. Several of those present insisted he should be logical and appoint someone to assume responsibility from that moment. To this he agreed, and was as good as his word, for shortly afterwards a paediatrician was appointed to the staff of his maternity hospital. There are now many such appointments, but the interests and range of duties of those holding them seem to vary. Thus in one teaching hospital which I visited recently the paediatrician does not, as the sister put it, 'interfere' with the management of normal infants but expects to be consulted only about the abnormal, the sick, and the premature. It is my belief he has got to interfere a great deal; perhaps even to establish the right to interfere. It cannot ever be assumed that because the baby is of normal development breast feeding will be easy. The obstetrician may leave the conduct of normal labour to the midwife, but he does recognize the possibility that uterine inertia may arise and has laid down explicit instructions to meet it.

Nursing Staff and Infant Feeding

Rather more open to question is the ideal constitution of the nursing staff for the kind of management I have outlined. In my own hospital it has been happily solved by the appointment of a sister whose duty it is to see that a careful examination of the breasts is part of the routine ante-natal care, and that the preparatory treatment is carried out. She lectures to the pupil-midwives on breast feeding and teaches them the detail of the use of the hands for the removal of milk, advises when suckling should be suspended, when oestrogen is called for, and so on. She works in the lying-in-wards in co-operation with their sisters, and attends the hospital infant welfare centre. She also has charge of the nursery for premature babies. It is a great asset that in addition to having taken her general and midwifery training she has also qualified as a health visitor and is thus inclined towards the longer view of the subject and is able to teach its importance. This arrangement seems to me to have advantages over the employment of a staff of specially trained nurses solely to tend the babies, for it retains their management in the hands of the pupil midwives, where surely it should be if there is to be any hope of improvement in their work when they undertake independent practice. There is an increasing tendency for various aspects of maternal and infant care to become detached from each other, even to be delegated to groups of special workers; as, for instance, in the care of the excessively premature infant. Against the convenience which this plan sometimes provides must be placed certain distinct disadvantages. An extreme example of the latter is the intrusion of the staff of the massage department into the lying-in-wards to deal with the overloaded breast. Inevitably this has the effect of suggesting to the ward staff that it is a task beyond their skill, instead of being, as I hold, one they should learn as an essential part of their training. At any rate what I have outlined is one plan, and after three years' trial we are satisfied it can be made effective.

Clinical Research

I have described this method of managing breast feeding in a maternity hospital in some detail because I am convinced that unless the problems surrounding the start are successfully solved we are unlikely to see any appreciable rise in the proportion of naturally fed infants. I do not doubt the plan can be improved and we are continually trying to devise improvements. This brings me to what I hold to be by far the greatest need of all; the need of clinical research. It is wholesome to remind ourselves that in its main principles the management of infant feeding today is almost exactly where Budin (1907) left it nearly half a century ago. It requires a considerable effort of imagination to realize how radical a change of method was his plan of putting a baby on the scales to find out how much milk it obtained when drinking at the breast. There are indeed hints in his lectures that, great man that he was, he did not find his task easy. Such innovations are usually resented. He saw the need to ascertain how much food a baby required to secure its growth and to supply any deficiency in a form that was safe. He was, in fact, determined to replace guesswork by measurement. He was greatly interested in lactation, and made careful observations on the variations in the yield of the wet nurses he employed for weakly infants; but it does not appear that he applied himself closely to the problem I have been considering, the instability of lactation. He was, however, dealing mainly with very ill-nourished women and starving babies; for you will recall his work was done in the eighties and early nineties of the last century, when France was suffering from her losses in the Franco-Prussian war, her birthrate was declining, and in her cities the rate of infant mortality often stood at 200 per 1,000. Budin set himself the tremendous task of finding means to check this huge wastage of infant life. If we exclude the discovery of vitamins and the control of scurvy and rickets which we owe to it, it is fair to say that beyond the many refinements in artificial feeding no notable

advance in method has been made in the last half century.*

It may be retorted that this delay is because it is only within the past ten years or so that physiologists have unravelled even some of the part played by hormones in milk secretion, and that until this point was reached no material advance was possible. Must we then wait passively until the whole story is unfolded instalment by instalment? The very fact that the present stage of knowledge was so long delayed contains its warning, for as Wilfred Trotter (1941) has reminded us, 'Physiology is an independent science which must follow its own inspiration, finding it sometimes here and sometimes there and only occasionally in medicine.' I should be much surprised to learn that any of its recent discoveries in lactation were inspired by concern for the fact that half this country's babies are artificially fed by the time they are three months old. To extend the quotation I have just read, 'It is on the most ordinary phenomena of medicine that the illumination of physiology is most dimly cast. . . . Medicine, more and more understanding the lost opportunities of past years, will take to itself the methods of experimental science and lead the *direct* attack on its own problems.' Here surely is a challenge. With the resources of the universities and the great teaching hospitals, can it be doubted such a direct attack would provide the enlightenment we need?

Other Aspects

There are many aspects of this subject on which I have not touched and about which there is almost everything to be learned; whether, for example, it is possible clinically to correlate what is known of the histological differences with the wide variations in the size of the breasts, and these again with differences in their capacity to yield milk. There is a type of gradual but still premature failure of milk secretion which, though I suspect it is often dependent on incomplete drainage, does not always seem to be so. This would repay study and might possibly be influenced by suitable additions of protein to the diet. The lactopoietic properties of thyroxin have scarcely been studied in the human. There are instances of the sudden cessation of lactation which are commonly attributed to emotional disturbance but on which there are few reliable observations. Upon the mechanism whereby milk is expelled from the breast, to which I have referred, there is clearly much more information needed, not only of its exact nature but of the possibility of its conditioning. On the side of administration there is a great opportunity to demonstrate the value of co-ordinating the work of obstetricians and paediatricians, of midwives and health visitors, and welding it into a truly effective unified service. The list could be enlarged to almost any extent and I am convinced that anyone applying himself to the subject would find problems interesting and worth while. Indeed, in accepting your invitation it was my hope that something in this lecture might enlist your help to raise this branch of preventive medicine to a standard worthy of its importance.

* In fairness I should mention that to Truby King we owe the demonstration that failing lactation can be augmented and a full yield can sometimes be reached when breast feeding has been interrupted, and even when it has been given up for a considerable period. I cannot be sure, however, that he realized this possibility to be closely dependent upon the degree to which involution has proceeded. The value of 'massage' of the breasts in bringing about a revival of secretion probably consists in emptying the duct system and evoking the expulsive mechanism, rather than in producing some local circulatory change, as he held. Nevertheless, whether his interpretation was correct or not his method was original and helpful. For our purpose it is worth reflection that it has proved of much more lasting value than all the energy he expended in the advocacy of breast feeding as a moral duty.

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THE TITRATABLE ACIDITY, pH, AMMONIA AND PHOSPHATES IN THE URINES OF VERY YOUNG INFANTS

BY

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It has now been established that for some time after birth the kidney is still functionally immature. In many respects its actions differ from those of the same organ in adult life. This is but one aspect of the physiology of infancy, but it is an important one in clinical medicine, and so illuminating have the findings been that there is every reason to prosecute further studies of the organ in the early days of life. It has already been shown that the glomerular filtration rate, the urea, and the sodium and chloride clearances are very low in newborn babies, and that very young animals are unable to concentrate their urines to the same extent as adults of the same species. These and other aspects of the subject were reviewed by McCance (1946); and since that time papers have been completed on the excretion of water, urea, and sodium chloride by the newborn rat (McCance and Wilkinson, 1947), and the excretion of diodone and creatinine by infants in the early days of life (Dean and McCance, 1947). There is almost no literature dealing with the subject matter of the present paper, but any pertinent observations will be referred to when the results are being discussed.

Methods

Samples of urine were obtained from healthy full-term babies born in the Landesfrauenklinik, Wuppertal. The urines passed immediately after birth were procured through the keenness and dexterity of the staff of the labour room; the remainder were collected in the usual way from male infants by strapping a small test tube over the penis. The urines were preserved under toluene in the ice chest for a few hours and were then taken to the I.G.-Farben laboratories where they were examined without delay for pH, titratable acidity, and ammonia. The urines were also analysed for inorganic phosphates, total nitrogen, and sometimes for urea, but it was not always possible to begin these determinations on the day the urines were received. If there was a precipitate of urates in the urines, it was customary to warm them before removing the aliquots for the determinations of the titratable acidity, ammonia, phosphates, and total nitrogen, but the pH was usually determined before the urine was warmed.

Specimens of urine were also obtained from healthy British men and women and from healthy well nourished Germans. These urines were collected at various times throughout the day. Some were early morning specimens. Aliquots were removed soon after the urines were passed for the determination of pH, titratable acidity, and ammonia, and the remainder of the urine was preserved under toluene if it was not possible to make the determinations of phosphates and total nitrogen forthwith.

Through the co-operation of the staff of the Kamillus Krankenhaus, Essen, some specimens of urine were also obtained from ketosed diabetics. These urines were preserved with toluene and sent to Wuppertal within a few hours, where they were treated in the same way as the other urines.

The pH was determined colorimetrically by the B.D.H. capillator method. For the determination of the titratable acidity 1 ml. of the urine was titrated with 0·01 N sulphuric acid in a white porcelain dish to pH 7·4. The end point was determined colorimetrically by removing very small drops with a fine glass rod and mixing them with phenol red on a white tile, and was checked by the B.D.H. capillator. Phenolphthalein was then added and the urine further titrated to the first appearance of a pink colour. This was usually pH 8·3 to 8·4, and if the urine was coloured or the end point difficult to see this was checked by the capillator using cresol red as the indicator. The ammonia was determined both by formol titration and also in Conway and Byrne (1933) 'units'; 1 ml. of 0·01 N HCl or 0·01 N H_2SO_4 was placed in the centre chamber and the back titration was carried out with approximately 0·01 N Baryta, or CO_2 free NaOH. The indicator used was a mixture of methylene blue and methyl red (Conway, 1935).

The result of the formol titration was taken as a rough guide to the quantity of urine to be taken for a gasometric determination of ammonia. All the figures for ammonia given in this paper were obtained by the diffusion method. The phosphates were determined either by the method of Briggs (1922) or of Fiske and Subberow (1925). Both gave the same results, but the latter method required less urine and was generally employed. A Pulfrich step photometer was used for all the colour comparisons. The total nitrogen was determined by the standard micro Kjeldahl procedure. Copper selenide was used to facilitate the digestion and heating was continued for at least one and usually many hours after the mixture cleared. Lee and Widdowson's (1937) method was used for urea. The urine was not always titrated twice to pH 7·4, but all other determinations were invariably carried out in duplicate. The proportion of the titratable acidity due to phosphates was determined in the following way: 1 ml. of a solution of KH_2PO_4 containing 2 mg. of P, was treated with small quantities of 0·01 N NaOH and the pH noted after each addition. From the results a curve was constructed showing the number of cubic centimetres of 0·01 N NaOH required to titrate from pH 5·4, 5·6, 5·8, 6·0 . . . to 7·4, and also to the phenolphthalein end point. From this curve, the pH of the urine, and the amount of P found in it, it was possible to calculate the contribution of the urinary phosphates to the titratable acidity. In doing so it was assumed that the constituents of the urine other than P did not materially affect its titration. The difference between the total titratable acidity and the titratable acidity due to the phosphates gave the proportion due to organic acids.

The data now to be set out and discussed are based upon the examination of seventy-two urines obtained from sixty-eight infants, forty-three urines collected from thirty-six adults, and ten specimens of diabetic urine. Two of the last came from the same patient, but the second was obtained some months after the first when the man was readmitted to the hospital. The composition of an infant's urine varies so much with its age that for some purposes the babies were divided into the following seven age groups. The first comprised ten babies from whom urine was obtained at or immediately after birth (age 0); the second, ten babies aged 5 to 24 hours; the third, ten babies aged 24 to 72 hours; the fourth, eleven babies between 72 hours and 4½ days; the fifth, eleven babies, aged 4½ to 6 days; the sixth, ten babies aged 6 to 7 days; and the seventh, ten babies aged 7 days or older. The majority of the babies in the last group were 7 days old, but two were 8, one 9 and one 12 days of age. The babies were all breast fed and the practice at the Landesfrauenklinik is to give the children nothing by mouth in the first few days of life except mother's milk. They are first put to the breast eighteen to twenty-four hours after birth. Some of the babies in the older age groups were being given a small supplement of half and half ' Haferschleim ' and cows' milk.

Results

pH. Henderson and Palmer (1914) found the average pH of 222 normal adult urines to be 5·98. The pH of the seventy-two infant urines averaged 5·96, and of the forty-three adult urines 6·11, which is almost the same, but as the frequency distribution diagram in fig. 1 shows, the pH values of the infant urines were more closely grouped about the mean than those of the adults, and there were fewer urines

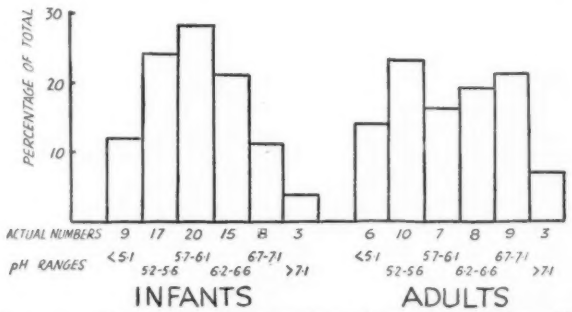

FIG. 1.—Frequency distribution diagrams of the pH values of infant and adult urines.

in the highest and lowest pH groups. This may just be an expression of the fact that the adults were subjecting their bodies to greater pH changes due to their more varied diets and activities, but it may also indicate that the pH of an infant's urine is not so easily changed by the kidney in response to variations in the pH of the internal environment.

The pH of the urine may be affected by the age of the infant. This was pointed out by Ylppö (1916) and by Thomson (1944), some of whose observations have been of great value in working up the present data. The results of the present investigation are given in table 1. None of the

TABLE 1

CHANGES IN THE pH OF THE URINE DURING THE EARLY DAYS OF LIFE

	Present data			Thomson's data	
Age	pH average value	Range	σ	Age days	Average value
0	6·06	4·9–6·8	0·71	1	5·70
5–24 hr.	5·70	4·9–6·3	0·32	2	5·80
24–72 hr.	5·70	5·0–6·3	0·45	3	6·12
72 hr.–4½ days	6·04	5·0–7·0	0·65	4	6·20
4½–6 days	5·90	5·1–6·7	0·49	5	6·41
6–7 days	6·10	5·1–7·7	0·82	6	6·40
7 days and over	6·30	5·5–7·4	0·76	8	6·58

differences are statistically significant owing to the large scatter at each age, but the figures do agree on the whole with those of Ylppö and of Thomson, whose average figures taken from the latter's fig. 11 are also given in table 1. It should be pointed out that Thomson had no group corresponding to the present age 0, and also that his observations, although showing a very great range of scatter, may be more valuable than the present ones, for they were based upon twenty-four-hour specimens. Thomson also demonstrated similar pH changes in the day-to-day urines of individual children, and it seems probable that there really is a tendency for the pH of the urine to rise from the first to the ninth day of life. Thomson's explanation of the phenomenon was that the newly born infants were in a state of acidosis, and, while this may be true, it does not seem a completely satisfactory explanation of the urinary findings. A number of authors have studied the serum chemistry of newborn infants, and some of them have compared their findings with those of adults (Lucas et al., 1921; Hoag and Kiser, 1931; Marples and Lippard, 1932, 1933; Branning, 1942). There is general agreement that the plasma bicarbonate is lower soon after birth than it is in adult life, and that there may be more organic acids in an infant's plasma, but there is no certain evidence that this acidosis corrects itself in the first eight or nine days of life. Hoag and Kiser (1931) stated positively that the plasma bicarbonate level was not affected by age up to the thirteenth day of life. Marples and Lippard (1932) considered that the plasma bicarbonate was lowest on the third day of life, but their figures are unconvincing and not in agreement with those of Lucas et al. (1921).

Ylppö (1916) showed that two days' starvation materially lowered the pH of the urine in older infants, and babies of one to three days of age must be regarded as being in a state of starvation. This, coupled with the progressive intake of metabolizable food after the second day, may be the explanation of the changes in urinary pH, but there would appear to be another one, and both may operate. The present results have shown that the urine passed at birth, which must have been formed in utero, may have a pH as high as 6·8, and the average for these specimens is higher than for those of the first and second days of life. These urines passed at birth are always very dilute (see later), but immediately after birth the infant enters a phase of hydropenia and oliguria, and this again is superseded by a period of rehydration and rising urine volumes as the flow of milk is established and increased (Veil, 1923; Thomson, 1944). Henderson and Palmer (1914) found a direct relationship between the pH and the volume of 122 twenty-four-hour specimens of adult urine. It is well known, moreover, in adult men and animals who have not taken food for some hours, that if the urine volumes are small the pH tends to be low and that a diuresis tends to raise the pH of the urine (Rüdel, 1892; Cushny, 1904; Carr, 1921; Briggs, 1942). Eggleton (1946) made similar observations. The same is true of infants (table 2), and it is suggested that the rate at which the urine is formed helps to explain why the pH of an infant's urine tends to fall for a day or two after birth and then to rise again for the next eight or nine days. It may be pointed out in passing that the pH of the urines formed in utero did not on the whole suggest that the infants were in a state of acidosis before birth or during that process. Only one of the urines was highly acid, but this may be because the infant's kidney can produce a very acid urine only when the pH of the internal environment has become highly abnormal. Possibly all infants, however, are able, given the requisite stimulus, to concentrate H ions in their urines nearly as well as adults, for a number of these infant urines have had pH values as low as 4·9, which is about the limiting value at any age.

Titratable acidity, total nitrogen, and ammonia. It is important to realize at the outset of any discussion on titratable acidity what the determination sets out to measure and upon what its magnitude chiefly depends. Urine is generally acid, and this is due to the fact that it contains an assortment of weak organic acids such as uric acid, lactic acid, β-hydroxybutyric acid, etc., and phosphates. The pH of the urine fixes the proportion of the last-named present as the dihydrogen salt, and also what fractions of the other weak organic acids shall be present as their salts, and what fraction as the free acids. The titration of any specimen of urine with NaOH gives a measure of the free hydrogen ions in it due to all these acids. It does not measure the acid radicles in the urine, most of which may be

TABLE 2

EFFECT OF DIURESIS ON pH OF URINE

R. A. M. Age 47 years ..	Min. Vol.	1·0	2·37	8·9	7·0	2·3	1·6
	pH	4·9	5·1	6·0	5·8	5·2	5·0
Baby R. Age 21 days ..	Min. Vol.	0·0116	0·0144	1·04	0·922	0·670	0·088
	pH	5·7	5·9	6·6	6·5	6·1	5·5
Baby T. Age 16 days ..	Min. Vol.	0·076	0·300	0·85	1·2		
	pH	5·3	5·5	6·1	6·3		

regarded as in combination with fixed base and/or ammonia. The titratable acidity in any specimen of urine depends mainly upon the following three variables.

(1) pH. It is clear that the pH must affect the titratable acidity, for if it is high enough the urine will contain no free acid and there will be nothing to titrate. The effect of pH is shown in table 4 with other pH effects which will be discussed later. The average titratable acidities of the infant urines show a steady fall as the pH rises. The differences between the first two pairs of the three adjoining pH groups were statistically significant ($t=2\cdot01$, $p=0\cdot05$; $t=2\cdot22$, p between $0\cdot05$ and $0\cdot02$). The difference between groups 1 and 4 was highly significant ($t=3\cdot2$, p between $0\cdot01$ and $0\cdot001$). For adults the differences between all three adjoining groups were statistically significant ($t=3\cdot2$, $p=0\cdot01$; $t=3\cdot3$, p between $0\cdot01$ and $0\cdot001$; $t=2\cdot75$, $p=0\cdot02$). The effect of pH, however, can be completely masked by the other two determinants and should not be considered in practice as the most important of the three.

(2) The concentration of the urine. This is a most important factor in isolated specimens, i.e. when the titratable acid per 100 ml. of these specimens is under investigation (see later), but it is probably not so important when the excretion of titratable acid/24 hours is the object of study.

(3) The quantity of phosphates in the urine. (Cushny, 1904; Hendrix and Sanders, 1923-24; Pitts, 1945a, b; 1946.) This is generally considered to be highly important and phosphates are usually spoken of as the main 'buffer acids' in the urine (Pitts, 1945a, b). The effect of phosphates seems to be exaggerated when they are given experimentally by injection, for they are then excreted much more rapidly than the accompanying base, and even the alkaline salt Na_2HPO_4 will greatly increase the titratable acidity of the urine (Cushny, 1904; Hendrix and Sanders, 1923-24). Creatinine also plays a minor rôle as one of the urinary buffer substances (Pitts, 1945a, b).

The ammonia found in the urine is now considered to be made by the kidney from glutamin in the circulating plasma (van Slyke and others, 1943), and to be excreted in response to acid substances left in the tubules after the reabsorption of fixed base (Briggs, 1942). It serves as a measure of this reabsorption, or of the strong acid radicles excreted by the kidney without corresponding fixed base. In other words, it can be taken as a guide to the capacity of the kidney to conserve fixed base.

Table 3 gives information about the acidity titrated to 7·4 and to the phenolphthalein end point, the total nitrogen, the ratio of the total N/acidity titrated to the phenolphthalein end point, the ammonia nitrogen, and the ammonia coefficient (ammonia N × 100/total N) in the infant urines and also in the adult specimens. It should be studied in relation to table 1, which showed the average pH's of the urines of the same age groups. It will be

TABLE 3

Age	Titratable acidity ml. 0·01 acid / ml. urine: to phenolphthalein end point	Titratable acidity ml. 0·01 acid / ml. urine: to pH 7·4	Total N ml. 0·01 NH_4OH/ml. of urine	Ratio Total N/acidity titrated to phenolphthalein end point	Ammonia N ml. 0·01 NH_4OH/ml. of urine	Ammonia coefficient
0	0·295 (0·14–0·74)	0·13 (0·04–0·40)	4·99 (2·16 – 9·2)	18·7 (8·9 – 32·6)	0·410 (0·21–0·72)	8·85 (2·9–12·6)
5–24 hr.	2·62 (1·05–5·40)	1·31 (0·55–3·75)	39·0 (19·1–58·8)	18·3 (5·2 – 40·0)	3·45 (1·03 – 5·8)	8·86 (2·8 – 15·2)
24–72 hr.	2·77 (1·20–5·50)	1·51 (0·48–3·70)	51·6 (21·8–97·3)	20·6 (8·9–27·4)	4·20 (1·70–8·20)	8·1 (5·0–12·4)
72 hr.–4½ days	1·63 (0·35–5·90)	0·85 (0·20–3·20)	28·5 (6·9–56·8)	22·3 (9·2–44·6)	2·19 (0·47–7·50)	8·3 (3·4–15·0)
4½–6 days	0·825 (0·30–1·48)	0·390 (0·15–0·65)	13·7 (6·4 – 27·4)	18·1 (8·5–32·3)	1·23 (0·41–1·95)	9·8 (5·0–16·3)
6–7 days	1·13 (0·35–2·85)	0·58 (0·00–1·90)	23·0 (3·26–52·0)	23·2 (9·3 – 54·2)	1·61 (0·27–3·40)	7·7 (4·0–11·3)
7 days and over	0·86 (0·30–1·75)	0·32 (0·00–1·10)	15·10 (6·4 – 27·6)	20·6 (10·9–45·6)	1·13 (0·39–2·75)	7·6 (1·9–11·0)
Adults	3·05 (0·60–10·4)	1·63 (0·00–7·20)	46·5 (18·7–107·0)	21·4 (4·81–69·3)	2·59 (0·30–7·80)	5·90 (0·8–15·6)

seen at once that there was a great change in the titratable acidity of the urines soon after birth. From 0·295 ml. 0·01 N NaOH/ml. of urine secreted in utero, it rose to 2·77 ml. between the twenty-fourth and seventy-second hours of life, and thereafter fell to a level of about 1 ml. If all the children are taken together it can easily be shown, as might have been expected, that the titratable acidity fell as the pH rose (see table 4), but the small changes in the pH of the urines of the different age groups (see table 1) were not responsible for the large changes in titratable acidity shown in table 3. These were mainly the result of changes in the concentration of the urine. This is shown by the figures for total N and for the ratio of titratable acidity to total N. If the total N be taken as a measure of the concentration of the urine, then it will be seen from table 3 that the titratable acidity varied with it, for the ratio of the total N/titratable acidity changed very little and in no consistent direction in spite of fluctuations in the quantity of total N per ml. of urine. These changes were due to the fact that the urine passed in utero was extremely dilute, whereas that passed during the first seventy-two hours of life was much more concentrated owing to the child being dehydrated at that time. The urines passed later in the first week of life were again more dilute (Heller, 1944; Thomson, 1944). It will also be noticed that, even when the infants were dehydrated and the titratable acidities were at their highest, the average value was lower than the mean for the whole group of adults, many of whose urines were, for adults, quite dilute. This is a demonstration of the fact that a baby is incapable of producing a urine with an osmotic pressure equal to that which an adult can produce under comparable conditions. Most of the concentrated adult urines had titratable acidities above 5 ml. of 0·01 N NaOH per ml. of urine. The inability of a baby to produce a concentrated urine, however (see p. 202), may not be the only reason why the titratable acidities of the infants tended to be so much lower than those of the adults.

The ammonia found in the urine of the infants in the different age groups is given in the penultimate column of table 3. It will be seen that the average values fluctuated with the age of the children, as did the titratable acidities and the total nitrogens—and for the same reason. The ammonia coefficients did not vary in any consistent direction with age during the first week of life; but they were, in all the age groups, higher than the average value for the whole group of adults. Brock and Hofman (1930) came to the conclusion that the ammonia coefficients of infants were high, but their work was done on babies older than those in the present series. Landsberger (1925b) has reported on one baby aged one day with an ammonia coefficient of 2·6, and Hottinger and Hottinger (1932) gave a very low figure for the ammonia excretion of a baby in the first few days of life, but no conclusions can be drawn from single cases. Taking the children as one group and the adults as another, the average coefficient for the babies was 8·466, $\sigma = 3·34$ and for the adults 5·40, $\sigma = 2·71$. The difference between the ammonia coefficients at the two ages was highly significant ($t = 5·10$, $p = < 0·001$), and the histiograms of the relationship are shown in fig. 2. There is reason to believe that the urine of

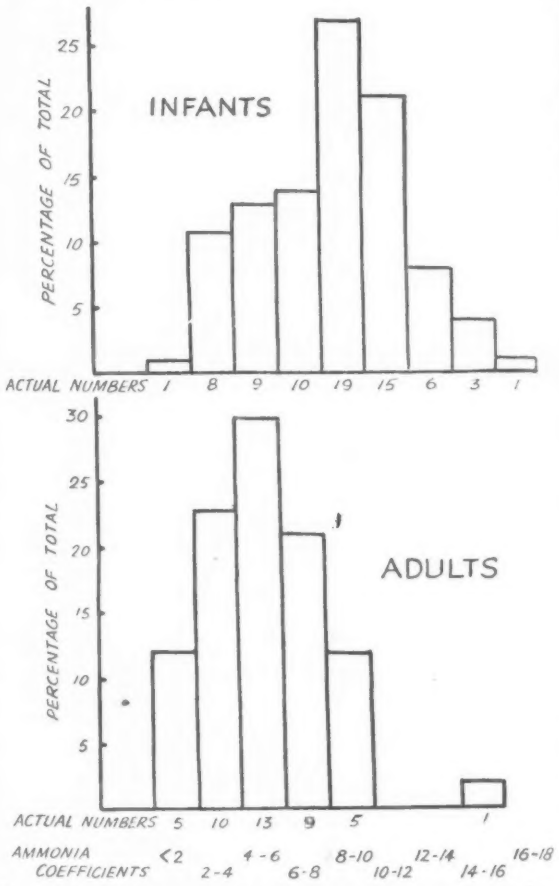

FIG. 2.—Frequency distribution diagrams of the ammonia coefficients.

infants may contain nitrogenous substances which do not appear in an adult's urine and that, therefore, the total nitrogen of an infant's urine may not be the metabolic equivalent of the total nitrogen of an adult's urine. The urea certainly forms a surprisingly small percentage of the total nitrogen in an infant's urine (Simon, 1911; and observations to be published), and had the relationship under discussion been based upon the ratio of the ammonia/ammonia + urea, there would have been a larger difference between the infants and the adults. The N partition in the urine of infants is under investigation. Henderson and Palmer (1914) came to the conclusion that the daily excretion of ammonia was little affected by the pH of the twenty-four-hour specimens, but Eggleton (1946) came to essentially

the opposite conclusion, which seems a more reasonable one. Hubbard (1923-24) considered that there was a closer correlation between the pH of the urine and the concentration of ammonia in it than there was between the pH and the quantity of ammonia excreted or the ammonia coefficient. It may be shown from the present data (see table 4)

TABLE 4

THE EFFECT OF pH UPON THE URINARY ACIDITY, TITRATED TO pH 8·3, THE AMMONIA COEFFICIENT, AND THE NH_3/ACIDITY TITRATED TO pH 7·4 AND 8·3 OF INFANTS AND ADULTS

Infants

	Group 1 up to pH 5·5	Group 2 pH 5·6 –pH 6	Group 3 pH 6·1 –pH 6·6	Group 4 pH 6·7 and over
Number in group	18	21	22	11
Titratable acidity to phenolphthalein end point	2·48 σ=1·95	1·52 σ=0·93	0·95 σ=0·76	0·58 σ=0·38
NH_3 coefficient	9·41 σ=3·1	8·74 σ=2·89	8·62 σ=2·98	5·8 σ=4·18
NH_3/tit. acidity to pH 7·4*	2·03 σ=0·87	3·46 σ=1·38	4·82 σ=2·08	6·47 σ=1·55
NH_3/tit. acidity to phenolphthalein end point	1·14 σ=0·32	1·62 σ=0·45	1·60 σ=0·50	1·54 σ=0·40

Adults

	Group 1 up to pH 5·0	Group 2 pH 5·1 –5·9	Group 3 pH 6·0 –6·9	Group 4 pH 7 and over
Number in group	5	14	16	8
Titratable acidity to phenolphthalein end point	6·70 σ=2·30	3·95 σ=1·50	2·23 σ=1·39	0·84 σ=0·39
NH_3 coefficient	9·88 σ=3·16	6·33 σ=1·22	4·25 σ=1·59	2·27 σ=1·12
NH_3/tit. acidity to pH 7·4*	1·31 σ=0·23	1·31 σ=0·35	1·99 σ=1·17	7·24 σ=3·90
NH_3/tit. acidity to phenolphthalein end point	0·89 σ=0·10	0·86 σ=0·15	0·83 σ=0·16	0·89 σ=0·41

* Omitting all urines from group 4 with pH = or >7·4.

that the ammonia coefficient fell both in infants and adults as the pH rose. The differences between the adult groups were all statistically significant. When the group up to and including pH 5·0 was compared with the next group, t=3·58, and p was <0·01, and when the pH 5·1 to 5·9 group was compared with the pH 6-6·9 group t=4·07 and p<0·01. For the two most alkaline groups t=3·2 and p 0·01. The differences between the adjoining groups of the infants were not statistically significant, but the difference between the most acid and most alkaline group was significant (t=2·77 with p between 0·01 and 0·02). There can be little doubt that at all ages the more acid the urine the more of the total nitrogen tends to be excreted as ammonia.

The present results do not support the old German contention (Simon, 1911; Landsberger, 1925a) that the urine contains very little ammonia for a day or two after birth, or that the ammonia coefficient is extremely low till the meconium has been passed, and then rises gradually as the flow of milk is established and bacterial fermentation in the gut produces organic acids to be excreted by the kidney.

The ratio of the ammonia to the titratable acidity. Early workers usually measured the titratable acidity by titrating the urine to the phenolphthalein end point, but later it appeared more physiological to most workers to titrate to pH 7·4 which is the approximate pH of the blood (Henderson and Palmer, 1914, 1915). Some have continued to titrate to pH 8·2 (Landsberger, 1925a, b; Eggleton, 1946) and Maizels and McArthur (1928-29) changed their end point from pH 7·4 to the phenolphthalein change. For anyone interested in the ammonia/titratable acid ratio, there is a sound reason for preferring the phenolphthalein end point to 7·4. Ammonia continues to be excreted in the urine, although in smaller amounts, even at pH values above 7·4; and consequently the ratio of the urinary ammonia to the acidity titrated to 7·4 rises with the pH and becomes infinity at 7·4. Table 4 shows this effect of pH. The difference between groups 1 and 2 for the babies was highly significant (t=3·80, p=0·001), the differences between groups 2 and 3 and 3 and 4 were also significant (t=2·52, p=0·02; t=2·05, p=0·05). The difference between groups 2 and 4 was highly significant (t=5·07, p=<0·001). The difference between the adult groups 2 and 3 was significant (t=2·09, p between 0·05 and 0·02); that between the groups 3 and 4 was highly significant (t=4·96, p=<0·001). This drift of the ratio with the pH would have been a great disadvantage in the present investigation in which it was proposed to compare the ratio in a group of infants and adults, for, although the average pH of the two groups was almost the same, the scatter was not (table 1). If, however, the urine is titrated to the phenolphthalein end point, for some reason, which may turn out to be of physiological importance, the ratio becomes independent of pH both in adults and infants (table 4), and, therefore, the

two ages may justifiably be compared. The ratio in adults averaged 0·86 (σ=0·21) and in infants 1·48 (σ=0·50). In infancy, therefore, the ammonia generally exceeded the titratable acidity, and this is in agreement with a few findings of Brock and Hofman (1930) in older infants. The difference between 0·86 and 1·48 was highly significant ($t=7·7$, $p=<0·001$) and the histograms are given in fig. 3. These results show that, of the total acid

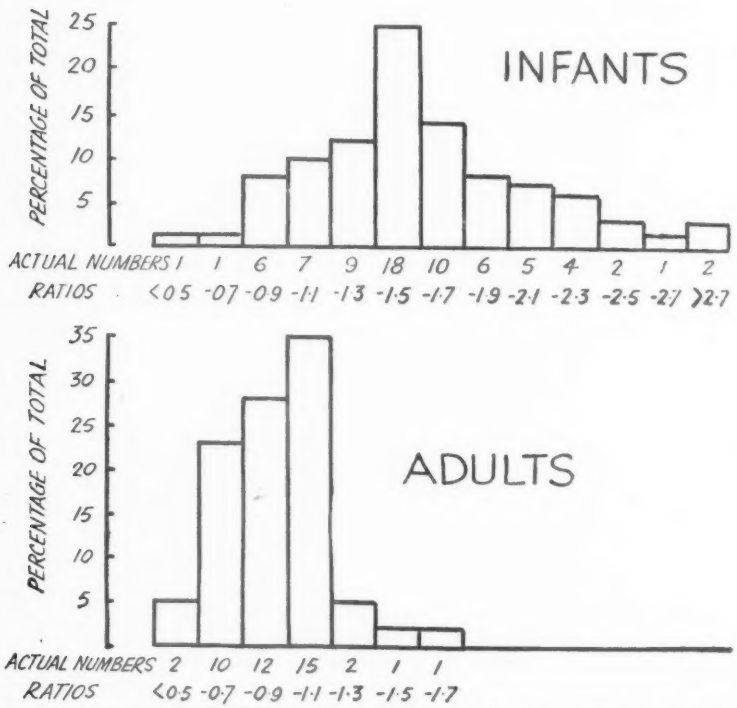

FIG. 3.—Frequency distribution diagrams of the ratios of the ammonia/acidity titrated to the phenolphthalein end point.

which is excreted by the kidney uncombined with fixed base, a higher proportion tends to be combined with ammonia in infancy than in adult life, and a smaller proportion to be found as free titratable acid. An explanation of why this should be so will now be given.

The excretion of phosphates. Phosphates do not stimulate the kidney to excrete ammonia (Marriott and Howland, 1918); but they may, as already stated, contribute a great deal towards the magnitude of the titratable acidity (Pitts, 1945a, b). It was natural, therefore, to look into the excretion of phosphates in newborn children and to compare the findings with those of adults. The percentage of phosphates in adult urines, and the phosphate clearances, have been found by others to be very variable and to be subject to unknown laws (Ollayos and Winkler, 1943; Pitts and Alexander, 1944). This has to some extent been confirmed, and it has been found to be true also of infants, but there is no doubt that there are big differences between the two ages in the way in which they excrete phosphates. The urine in infancy may contain practically no phosphates. Figures below 1 μg. per ml. of urine were obtained on three of the children. The highest figure was 780 μg. per ml. but this was quite exceptional and there were only two others over 400 μg. per ml. There seem very few figures in the literature with which to compare these. Maizels and McArthur (1928-29) found urinary phosphates in older and frequently pathological children to range from 0·045 per cent. to 1·46 per cent. as P_2O_5. They stated that 0·3 per cent. was about the upper limit of normality. Branning (1942) found the urine of a group of premature but 'older' babies to contain 0·33 to 1·8 g. of phosphorus per litre. These figures seem high, but the results may be expressed as P_2O_5 and the children were not really comparable with those in the present series. The average amount of phosphorus found in the infants' urines was 74·4 μg. per ml. and this is to be compared with 613·6 μg. per ml. in the adult urines. This difference, however, was largely due to the urine being so much more dilute in infancy. All the urinary constituents were present in smaller concentrations (compare the titratable acidity and total nitrogen). So far as phosphorus is concerned a much more valuable comparison between the infants and adults may be made by considering the P/N ratios. This virtually eliminates the differences due to the dilution. The ratio averaged 2·92 for the whole series of infant urines and 12·64 for the adult urines. The histogram of the relationship is shown in fig. 4. In proportion to the nitrogen it is clear that infants tend to excrete very little phosphorus, and from what is known about the urea clearances in infancy and about the serum phosphorus it is evident that the phosphate clearances are likely to be very much lower than they are in adult life. Preliminary results indicate that this is so, and the matter is now under investigation.

The small amounts of phosphates in infant urines naturally affect the 'make up' of the titratable acidity. The proportion of the titratable acidity due to phosphates was very much lower in infants than it was in adults. The proportion due to organic acids, therefore, was very much higher. Age up to the seventh day made no consistent difference to this, so all the children have been taken in one group for comparison with the adults. The results are summarized in the histogram given in fig. 5, and show that the proportion of the titratable

acidity due to organic acids tended to be very high in these infants. Hottinger (1925) found the 'organic acids' excreted per kilo of body weight to be higher in infants than in adults, but his only figures for two babies with ages similar to those of the present series were within the adult range. His data, however, are not really comparable. The nature of these 'organic acids' or organic buffer substances is obscure, but it is possible that an examination of the 'undetermined N' in infant urines, which has now been undertaken, may help to solve the problem. It will be clear from previous work (Marriott and Howland, 1918; Pitts, 1945a, b) and from what has already been said, that the small amounts of phosphates available for excretion in infancy may limit very materially the amount of free acid which their kidneys can excrete, and this no doubt explains, in part at any rate, why the ammonia coefficients are so high, for in the absence of buffer substances in the urine there would naturally be a tendency for acid substances to be excreted in combination with ammonia. If, moreover, it is correct that infants are in a state of acidosis during the early days of life (Ylppö, 1916, 1923-24; Seham, 1919; Hoag and Kiser, 1931; Branning, 1942), the acidosis may be explained by the paucity of phosphates available for excretion, for without them the ability of the kidney to excrete acids, and so to correct an acidosis, must be curtailed (Pitts, 1945 b, 1946).

Ketosed adults. The urines of ketosed adults make an interesting comparison with those of normal infants. Only ten have been obtained, but they are enough to bring out certain resemblances and differences. The data are set out in table 5. The urines of the adults who were ketosed had, as might have been expected, a lower average pH than those of the infants or of the normal adults. The total nitrogen in these urines was slightly higher than that of the normal adults, but this difference was not significant. The titratable acidity was slightly higher, and the phosphorus considerably lower. This led to a P/N ratio approximating to that of the infants, and meant that the percentage of the titratable acidity due to organic acids was higher than the adult normal and near the average for the infants. Thus the urines of the normal infants resembled in composition those of adults who were suffering from acidosis. The ammonia coefficients and the ratios of ammonia/titratable acidity of the ketosed adults were much higher than those of the normal adults and higher than those of the infants. In both instances the average for the infants fell between the normal adults and the ketosed adults. This indicates that, so far as the formation and excretion of ammonia were concerned, the infants were again reacting as though they were adults with an acidosis, but the same result might equally well be attributed to a deficiency of phosphorus available for excretion.

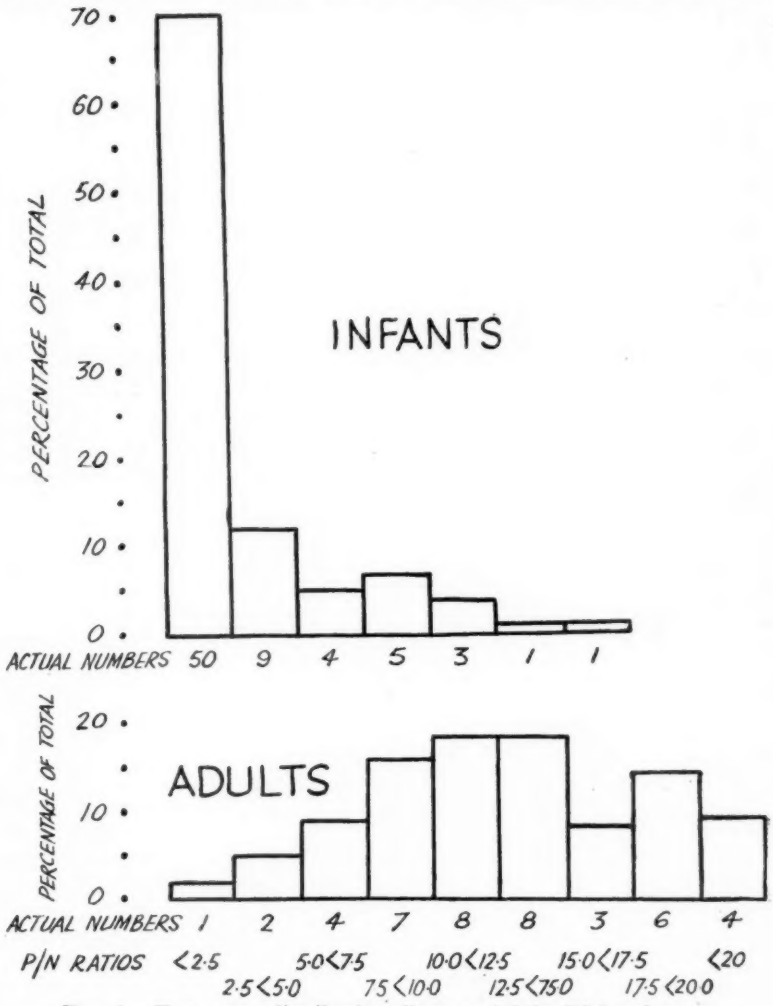

FIG. 4.—Frequency distribution diagrams of the P/N ratios.

The present results do not prove that the infants were in a state of acidosis. The pH of their urines, indeed, suggests that they were no more acidosed than normal adults. It is clear, however, that they were excreting so little phosphorus in their urines that their kidneys were forced to react in other ways as though they had an acidosis. It is also clear

that, if for any reason infants were to acquire an acidosis, the small amount of phosphorus available for excretion would greatly limit the capacity of their kidneys to correct it.

Foetal urine. Considerable interest is attached to the composition of urine secreted by the kidney in utero. It has been studied previously by Guthmann and May (1930) and by Tausch (1936). The latter catheterized a large number of babies at birth and made a great many observations on the colour, reaction, specific gravity, and total nitrogen. With his results the present data are in substantial agreement. The striking thing about these urines is their high dilution and low specific gravity. These may be due to the imbibition of liquor amnii (Smith, 1945), but in any event they are to be contrasted most strongly with the maternal urines, and with the urines passed by the same children twenty-four to forty-eight hours later. Tausch found the average total nitrogen to be 0·155 per cent., which seems very low in comparison with the specific gravities which he reported. The average total N for the present series of ten was 0·075 per cent.; the titratable acidity to phenolphthalein was 0·295 and the ammonia coefficient 8·85. The phosphorus averaged 6·16 μg. per ml. and the P/N ratio 1·22; 88·4 per cent. of the titratable acidity was due to organic acids. In all these respects the foetal urines resembled the urines passed by the babies after birth and differed only in greater dilution. It is hoped to make a much more complete study of urine passed by full-term infants while they are still in utero.

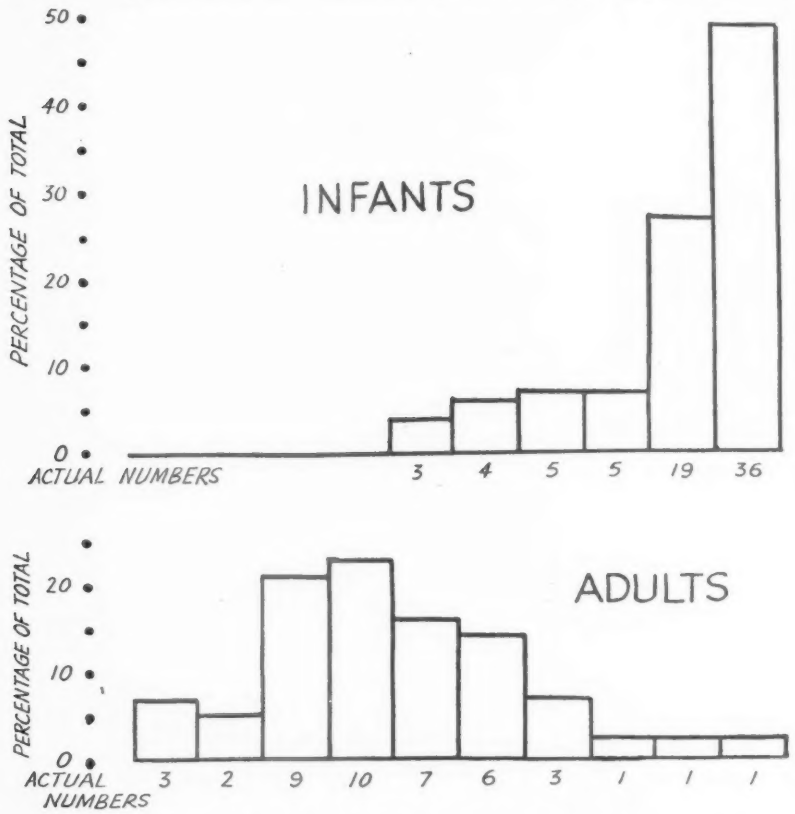

FIG. 5.—Frequency distribution diagrams of the percentage of the titratable acidity (endpoint pH 8·3) due to organic acids.

Summary

1. The average pH of infant urines tended to fall slightly after birth and rose again as the flow of milk became established. These differences were not statistically significant. The average pH of seventy-two newborn urines was almost the same as that of a collection of forty-three urines from healthy adults.

2. The acidity titrated to the phenolphthalein end point and the ammonia N of infant urines rose and fell with the total N, that is to say, with the concentration of the urines. They were, therefore, affected by the age of the children and were highest between the fifth and seventy-second hours of life. The titratable acidity fell as the pH rose.

3. The ammonia coefficients were unaffected by age, fell as the pH rose, and on each of the first seven days of life averaged more than those of normal adults.

4. The ratio of the ammonia to the acidity, titrated to the phenolphthalein end point, was unaffected by pH in both infants and adults and tended to be considerably higher in the former than in the latter.

5. The urines of newborn children contained very little phosphate and the phosphorus/nitrogen ratios were low by adult standards. In consequence of the small phosphate excretion the percentages of the titratable acidities due to organic acids were very high, much higher than in adults.

6. In their ammonia coefficients, ammonia/titratable acid ratios and P/N ratios, and in the percentages of the titratable acidity due to organic acids, the urines of newborn infants have been found

TABLE 5

A COMPARISON OF THE URINES OF KETOSED ADULTS WITH THOSE OF INFANTS AND NORMAL ADULTS

	Infants	Adults	
		Ketosed	Normal
pH	5·96 σ=0·63	5·4 σ=0·53	6·11 σ=0·83
Titratable acidity to the phenolphthalein end point ml. 0·01 N acid/ml. urine.	1·44 σ=1·33	3·23 σ=0·94	3·05 σ=2·23
Total N ml. 0·01 N NH_4OH/ml. urine.	25·0 σ=19·7	50·3 σ=29·9	46·5 σ=19·7
Ammonia coefficient	8·47 σ=3·34	13·9 σ=9·0	5·4 σ=2·71
Ammonia/acidity titrated to the phenolphthalein end point	1·48 σ=0·50	2·07 σ=1·34	0·86 σ=0·21
Phosphorus µg. per ml.	74·4 σ=134·5	323 σ=274	614 σ=316
P/N ratio	2·92 σ=3·8	7·11 σ=5·73	12·64 σ= 6·1
% of titratable acidity due to organic acids	86·2 σ=15·0	70·1 σ=20·5	42·1 σ=18·8

to resemble those of ketosed adults. This does not necessarily mean that the infants were suffering from acidosis, for the resemblances might equally well have been brought about by the small amounts of phosphorus available for excretion.

7. The small amount of phosphate normally excreted by the kidney would, however, severely limit the capacity of infants to deal with an acidosis if they had one.

8. Urine passed in utero is highly dilute, but differs in no other ways so far discovered from urine passed in the first few days of life.

The authors are indebted to Prof. K. J. Anselmino for allowing them to make use of the facilities at the Landesfrauenklinik, Wuppertal. Dr. R. F. A. Dean very kindly catheterized the babies and carried out the two experiments shown in table 2, and Dr. E. M. Widdowson has been a great help on many occasions.

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THE INTERRENAL SYNDROME IN CHILDHOOD

BY

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FUNCTIONAL PATHOLOGY

The adrenal cortex acts by the elaboration of a series of hormones which include among their functions the regulation of the electrolyte balance; carbohydrate, fat and protein metabolism; the development of the secondary sexual characteristics; and possibly the development of the gonads themselves. Although the action of many of these hormones is regulated by the pituitary, the latter gland has apparently little influence on that function of the adrenal which is essential for life, namely the regulation of the salt and water balance. An adrenalectomized animal quickly dies of the symptoms of Addison's disease, whereas hypophysectomy has not the same fatal outcome. This is in keeping with the generality that processes essential for life are, to a degree, autonomous (Swann, 1940).

The adrenal cortex is in a constant state of growth which takes place from without inwards. Throughout life new cells are being formed by multiplication of cells in the zona glomerulosa and from indifferent cells included in the capsule. The stage of growth takes place in the short zona glomerulosa. The cells then migrate inwards, forming the zona fasciculata, in the inner part of which and in the outer part of the ensuing zona reticularis the cells discharge their lipoid contents, possibly in part into a real glandular lumen continuous with the medulla (von Lucadou, 1938). The cells finally degenerate in the inner part of the reticulate zone (Zwemer et al., 1938).

After hypophysectomy the adrenal cortex atrophies in the reverse direction to which it grows. The atrophy progresses from within outwards. No definite histological abnormality occurs in the outermost zone (Crooke and Gilmour, 1938). It is to be presumed that this glomerular layer secretes the ' salt and water ' hormone (Swann, 1940). Our own investigations on the appearance of doubly refractile lipoids in the adrenal cortex have shown that this takes place initially in a narrow zone in the region where the zona glomerulosa changes into the zona fasciculata.

In states of hyperfunction of the cortex, the resulting clinical and metabolic picture depends on the nature and amount of the hormones produced. Haymaker and Anderson (1938) suggested there were two syndromes, the adrenogenital, associated with virilism and representing the excessive production of androgens; and the adrenocortical, associated with the clinical picture of Cushing's syndrome and the excessive production of cortin. These views have been supported and elaborated by Albright (1942), who concluded that the adrenogenital syndrome was due to an abnormal production of a ' N ' hormone which, having an action similar to testosterone propionate, was produced in normal individuals after puberty concomitant with an increased excretion of 17-ketosteroids and was concerned with somatic and secondary sexual development. The adrenocortical syndrome, according to this author, was due to an excess of ' S ' hormone which, acting by the inhibition of the synthesis of tissue, promoted the conversion of protein into sugar (glyconeogenesis) and inhibited the oxidation of glucose at the periphery.

The relationship between virilism and cortical hyperfunction is obvious. The aetiology of Cushing's syndrome was rendered debatable by the occasional occurrence of a basophil adenoma of the pituitary in this disease. However, Anderson and Haymaker (1937) were able to prolong the life of adrenalectomized rats by the injection of sera from two patients with Cushing's syndrome. Occasionally there is a disturbance of the electrolyte pattern the opposite to that occurring in Addison's disease (McQuarrie et al., 1937, Willson et al., 1940). Albright et al. (1941) produced amelioration of symptoms by giving testosterone, which is known to inhibit cortical function. The consensus of opinion is that Cushing's syndrome is due to adrenal cortical hyperfunction, the primary cause for which may arise either in the gland itself or be caused by an excess of adrenotropic hormone engendered by pituitary dysfunction.

The site of production of these groups of hormones is more speculative. Grollman (1936) considered

that the androgenic hormones were produced by the transient cortex, which he compared with the X zone of the mouse. One has, however, to be cautious in considering the transient human cortex as homologous with any zone in other animals, because the whole process of late foetal and early post-foetal remodelling of the adrenal cortex in human beings is unique and differs from the development of the suprarenals in all other mammals.

Cahill et al. (1942) tried to correlate the hormonal changes with alteration in the cytology of the adrenal cortex. Tumours associated with hormonal change could not be identified with any particular zone, but the degree of vacuolation of the cortical cells was roughly proportional to the severity of the hormonal disturbance. The more the syndrome approached the Cushing type, the more marked was the amount of vacuoles which were present. Fuchsinophil staining of the cytoplasm was present in all tumours but was more pronounced in cases with hormonal syndromes. From the remarks of these authors that the fuchsinophil staining of the cytoplasm was in some cases diffuse, in others in granules, it is evident that their interpretation of the Ponceau-Fuchsin stain is different from that of Broster et al. (1938). The latter, who correlated the presence of fuchsinophil granules in the cells of the adrenal cortex with virilism, considered the presence of this fuchsinophil material to be related to the presence of androgen.

CASE MATERIAL

Unless otherwise stated, the cases recorded were collected from the records of the Children's Hospital, Birmingham, during the last ten years.

Classification

For the purposes of description it is proposed to use the following classification and terminology:

ADRENOGENITAL SYNDROME

1. In the neonatal period.
   (a) Pseudohermaphroditism in girls.
   (b) Hyperplasia in boys.
2. In later childhood.
   (a) Macrogenitosomia praecox in boys.
   (b) Macrogenitosomia praecox with masculinization in girls.

ADRENOCORTICAL OBESITY (Cushing's syndrome)

The Adrenogenital Syndrome in the Neonatal Period

Females born with adrenal hyperplasia show pseudohermaphroditism characterized by a clitoris enlarged to such a degree that it is usually considered to be a penis and the infants are registered as boys. The external orifice of the urethra may be at the tip of the penis or more towards its base as in hypospadias. There is usually no external vaginal orifice. A uterus of normal infantile dimensions with Fallopian tubes is present. The ovaries are in the usual site, the size being normal or reduced. As a rule a rudimentary vagina is found opening into the urethra. The scrotum may be bifid, but in many cases it is normal except for the absence of testicles. Thus the external genitalia may give rise to no suspicion that the individual is other than masculine in sex. In males there are no external abnormalities.

In neither sex do the infants thrive. Vomiting and diarrhoea are usually the predominating symptoms, with a tendency to sudden collapse which responds to the administration of saline or cortical extract. Such cases have been described by Di Ruggiero and Jolly (1938), Butler et al. (1939), Dijkhuizen and Behr (1940), Thelander and Cholffin (1941), and Skelton (1945). Both Butler et al. and Thelander and Cholffin considered the symptoms to be due to a deficiency of cortical hormone of the nature of Addison's disease. They demonstrated a low serum sodium and chloride with raised serum potassium. Butler's case was unusual in that a brownish pigmentation occurred all over the body at the thirteenth day. Thelander (1946) kept his patient alive until the age of seven with the aid of salt and desoxycorticosterone acetate therapy.

Female pseudohermaphroditism in the neonatal period (cases 1-5).

FAMILY HISTORY. In one case a sib, thought to be a hermaphrodite, had died in infancy from 'pyloric stenosis.'

HISTORY. Apart from one case which did not thrive from birth, the remainder took well and appeared to be satisfactory for the first seven to fourteen days, when they were found to be not gaining weight. Vomiting occurred in all cases. In one it was associated with diarrhoea and was considered to be due to a parenteral infection. In a further two it was not severe, but in two it was a dominant symptom and both cases were admitted with the provisional diagnosis of pyloric stenosis. All the infants gradually deteriorated. Ages at death were 17, 25, 35, 44, and 82 days. In two cases where radiographs were taken there was no premature ossification in carpus or tarsus.

MORBID ANATOMY. The external genitalia, except for a posteriorly incomplete prepuce, were of normal male type in one case. There was a definite hypospadias in four cases. The scrotum was recorded as being bifid in two cases. The vagina did not open externally except in one case, where it was situated posteriorly to the clitoris, was 2·4 cm. in length, and enclosed the vaginal portion of the cervix of the uterus. In four cases where the

internal genitalia were mentioned, these consisted of a normal uterus, ovary, and Fallopian tubes.

The adrenals were hypertrophic, in some cases being larger than the kidneys. The surface was grossly corrugated. One was weighed and two were measured. In the one case the weight was 6·5 g. for the right and 6·4 for the left adrenal. Normal weights are less than 7·0 g. for both adrenals (Dietrich and Siegmund, 1926). The size was larger than that of the kidney in two cases, and almost the size of the kidney in one case (Plate Ia). The normal size is about one-third that of the kidney.

The thymus was considered to be atrophic in two cases. In the others it was normal.

Body measurements were taken in two cases and were found to be normal, both with regard to length and proportion.

HISTOLOGICAL FINDINGS. The adrenals were examined in four cases. The transient and permanent cortex were present in varying amounts. The cytoplasm was mainly granular in both transient and permanent zones. In the case living for eighty-two days the cytoplasm was predominantly vacuolated. The Ponceau-Fuchsin stain was slightly positive in the oldest case, negative in the remainder.

The thymus was normal in one case. A second contained Hassal corpuscles which were occasionally enlarged.

The histology of the remaining organs contained nothing relevant.

Hyperplasia in boys in the neonatal period (cases 6-10).

FAMILY HISTORY. This was in all cases negative.

HISTORY. In three cases the initial symptom had been vomiting starting on the first, fourth, and tenth days of life respectively. There was an associated failure to gain weight. One case was weaned at three weeks because of failure to thrive, and developed diarrhoea four days later. The fifth case developed diarrhoea when twenty-five days old, and vomiting when thirty days old. On admission two cases, of which one had rapid respirations, were reported as being shocked. Three cases collapsed suddenly and died. A further case collapsed several times before death. Ages at death were 21, 23, 28, 35, and 45 days. In one case, and also in one of the female pseudohermaphrodites, repeated examination of the urine showed a persistance of chlorides in normal amounts in spite of intractable vomiting. Of three cases radiographed for premature ossification, only one showed a carpal centre just appearing at the age of twenty-one days.

MORBID ANATOMY. The adrenals were hypertrophied, being usually as large as the kidneys. The surface was corrugated. The maximum weight of a single gland was 11·5 g. The thymus was reported as atrophic in three cases, but no weights were given. The prostate was considered to be enlarged in three cases, in one case weighing 2·3 g. In three cases the testes were weighed, the combined weights being 2·3 g., 2·27 g., and 3·8 g. respectively. Body measurements taken in three cases were normal and proportional.

HISTOLOGICAL FINDINGS. The proportion of transient to permanent cortex was variable. The cytoplasm was on the whole granular. When vacuolation occurred it tended to be in the permanent cortex. The Ponceau-Fuchsin stain was positive in two cases and slightly so in a third.

The testes, examined in two cases, were of the immature type normal for the age. The thymus, examined in one case, contained Hassal's corpuscles, of which some were unusually large.

Adrenal hyperplasia was found on five occasions in association with other conditions, twice in haemolytic disease of the newborn, twice with exomphalos, and once with glycogen storage disease. In none of these cases was there any abnormality of the sexual organs.

Haemolytic disease of the newborn (cases 11-12). One case was a still-born male hydrops foetalis; the other was a male icterus gravis with haemorrhagic diathesis who died at the age of ten days of a severe widespread interstitial and haemorrhagic alveolar pneumonia. In both cases the adrenals were the size of the kidneys.

Histologically, in the case of the hydrops, the cells of the zona glomerulosa, zona fasciculata and transient cortex contained large vacuoles. Fuchsinophil granules were absent.

The cytoplasm of the adrenal in the case of icterus gravis was granular. The cells of the transient cortex nearly all contained fuchsinophil granules. Fuchsinophil granulation was scanty in the permanent cortex. The thymus in the latter case was peculiar in that the lymphoid tissue of the cortex was almost absent. The Hassal corpuscles were numerous, numbering approximately eight per high-power field.

Exomphalos (cases 13-14). In the first case a boy died aged one day after an attempt at operative repair. The second case died aged eighteen days having deteriorated gradually. In both cases the thymus was normal in size.

Histology of the adrenal in the first case showed the zona glomerulosa to be vacuolated and Ponceau-Fuchsin negative. In the zona fasciculata and transient cortex the cytoplasm was granular and took the Ponceau-Fuchsin stain.

In the second case, which had a normal uterus, ovary, and Fallopian tubes, the cortical cytoplasm showed moderate vacuolation; granulation was slight and fuchsinophil staining moderately positive.

Glycogen storage disease and hyperplasia of the adrenals (case 15). A further case of adrenal hyperplasia was found incidentally in a still-born full-term male. The adrenals weighed 5·9 g. and

7·35 g. The tarsus contained ossification centres in calcaneus and talus. The thymus was normal. The liver weighed 200 g.

HISTOLOGICAL FINDINGS. The adrenal showed a well developed permanent cortex with a partly granular, partly vacuolated cytoplasm. The Ponceau-Fuchsin stain was slightly positive.

The liver cells were swollen, their outlines stained darkly, thus giving an impression of a cell membrane as in a plant cell. The cytoplasm was colourless with scattered groups of amphophil granules. The Best carmine stain showed most of the cells packed with carmine-positive granules although no special glycogen fixative had been used. These granules showed also a positive iodine reaction for glycogen (Plate Ib and c).

The Adrenogenital Syndrome in Later Childhood

Macrogenitosomia praecox in boys. Macrogenitosomia praecox in boys is relatively rare. Wilkins et al. (1940) collected from the literature eleven cases due to tumour. Their case was the first due to hyperplasia which had come to autopsy. A further case due to hyperplasia was reported by Thelander (1946). Although the tumours are usually carcinomata and run a short course, it is possible that hyperplasia may occur without a fatal outcome. Cahill et al. (1942) reported two boys who had had signs of macrogenitosomia praecox for seven or eight years. Both had reached the stage of fusion of epiphyses with resulting dwarfism.

Typically, boys with the adrenogenital syndrome show accelerated muscular and secondary sexual development with advanced ossification and excessive secretion of 17-ketosteroids. The prostate is hypertrophied, but the testes enlarge only slightly if at all and remain immature. If these cases do not die, the epiphyses fuse prematurely with consequent stunting.

The following case is reported by kind permission of Mr. E. R. Flint and Professor M. J. Stewart of Leeds.

Case 16. B. C. was admitted at the age of 2 years.

FAMILY HISTORY. The parents were cousins.

PERSONAL HISTORY. The birth weight was 7¾ lb. The boy sat up at seven months, walked at sixteen months, and began to say odd words at eighteen months. His general intelligence was thought to be not quite up to normal. He had always been a large child. Two months before admission he was thought to be developing too quickly, hair had appeared on the pubes, and the genitalia had enlarged. For some weeks spots had been noticed on his chest. He used to 'touch himself'. The bowels were generally constipated. Recently there had been some diarrhoea.

EXAMINATION. Examination showed a muscular child, height 36 in., weight 43 lb. He looked to be about five years old. His voice was deep for a child. In the ward he was strong and active. There was hair on the pubes, and the genitalia were enlarged and the testes descended. The penis erected on stimulation but there was no seminal secretion. A radiograph of the skull showed no abnormality. Fasting blood sugar was 90 mg. per 100 ml. Blood pressure was 105/75 mm. Hg. (Plate Id).

A laparotomy was performed. Both adrenals were found to be enlarged. The left was removed and weighed 12·9 g. Death occurred twelve hours after operation.

MORBID ANATOMY. The right adrenal weighed 12·3 g. Weights of testes were: left, 1·85 g.; right, 1·21 g. The prostate was larger than normal, weighing 3·37 g. The thymus was fleshy and succulent, weighing 32 g. The tonsils were slightly enlarged. The mesenteric glands and Peyers' patches were enlarged and hypertrophied. In the duodenum there was an acute healing ulcer 3 mm. in diameter on the anterior surface 8 mm. below the pylorus. The ventricles of the heart were both hypertrophic. The remaining organs were normal.

HISTOLOGICAL FINDINGS. Large areas of the adrenals had the structure of transient cortex. Such vacuolation as was present was confined to the zona glomerulosa. In the latter, only an occasional cell with a positive Ponceau-Fuchsin stain was seen, but those of the zona fasciculata were positive and took the stain with the same intensity as the transient cortex. The stain was much brighter in the operation specimen. The colouring of the autopsy specimen was more of a brick red shade.

The thymus showed a sharply demarcated and well developed cortex and medulla. An occasional haemorrhage was seen in the cortical zone. There were 1-12 Hassal's corpuscles per lobule, ranging in size from 13 to 181 microns (Plate IIe).

The prostate had the structure of an adult gland with numerous large alveoli separated by narrow septa. The mucous membrane was folded with papilliform processes and high columnar epithelium.

The testes measured 14 mm. by 5·5 mm., and 19 mm. by 9·4 mm. They contained several adrenal rests of the foetal type, measuring up to 2·5 mm. in diameter, which took the Ponceau-Fuchsin stain with the same brick colour as the adrenal taken from the autopsy. The structure of the testis was otherwise normal for a child. The epididymis and vesiculae seminales were normal.

A differential cell count was made of the pituitary after the method of Rassmussen and Herrick (1922). In 17,000 cells there were: eosinophils 50 per cent., basophils 2·5 per cent., chromophobes 47·7 per cent.

The vesicles of the thyroid were large and filled with colloid. The one parathyroid examined was normal, consisting entirely of water-clear chief

cells. The duodenum showed a healed ulcer. The remaining organs were normal.

Macrogenitosomia praecox in girls. Macrogenitosomia praecox in girls presents a varying degree of masculinization. The mildest cases show little more than hypertrophy of the clitoris. The most severe present a picture of pseudohermaphroditism so advanced that the individuals are reared as boys, the hypertrophied clitoris being mistaken for a hypospadic penis and the labia majora for empty scrotal sacs.

Case 17. D. J. had been brought up as a boy. He was admitted to the surgical side at the age of 6 years 10 months for the repair of a complete hypospadias. He had the features of a child of 12 or 14 years. The 'penis' was well formed and there was a complete hypospadias, the urethral opening being one inch below the root of the 'penis.' There was a small empty 'scrotum.' Pubic hair was well marked. Some axillary hair was also present.

A suprapubic cystotomy was performed. 'His' condition initially remained good, but he collapsed eighteen days after the operation and died four days later. At autopsy the pelvis contained a vagina leading to an infantile uterus, Fallopian tubes, and ovaries. The suprarenals were enlarged. The thymus appeared normal. No other abnormality was detected.

HISTOLOGY. The adrenals had the structure of the transient cortex except for a narrow zona glomerulosa. Only in the latter zone were vacuoles present. Sections stained with Ponceau-Fuchsin showed the cortex to be packed with fuchsinophil granules (Plate IIf).

Case 18. E. B., aged 11 years, had previously attended the hospital when five months old with an imperforate vagina. Recently she had developed some hoarseness of the voice and her general interests had been more those of a boy than a girl.

General examination showed the child to be big for her age, her features slightly masculine, and the skin coarse. The trunk had a male contour (Plate IIg). The mammary glands were undeveloped but the nipples were normal. The external genitalia showed a female distribution of pubic hair which was excessively present for a girl of this age. The vulva appeared normal but the clitoris was much enlarged. The child had no vaginal orifice. The opening of the urethra was in the perineum and situated at the base of the clitoris. No testes were palpable in the inguinal canals. On rectal examination a small hard mass, thought to be the uterus, was palpable anterior to the rectum. The 24-hour urinary 17-ketosteroid excretion was 28·7 mg. A radiograph of the carpus showed eight well developed centres. The pisiform bone was large. The secondary centre at the base of the first metacarpal had already fused with the shaft (normal 14 to 21 years).

An exploratory laparotomy revealed two normal ovaries, Fallopian tubes, and a uterus which appeared infantile but was normal as far as the cervix. There was no evidence of a vagina. The right suprarenal appeared normal in size and shape, but the left suprarenal was considerably enlarged. This enlargement appeared to be a general hyperplasia of the suprarenal rather than an adenoma.

A left suprarenalectomy was subsequently performed. Convalescence was stormy.

Table 1 gives the serum electrolyte levels taken before, twelve days after, and twenty-six days after the adrenalectomy.

Thirty days after the operation the daily urinary 17-ketosteroid excretion was 27 mg. A month later this had fallen to 17·2 mg., but eight months after the adrenalectomy it was 29·7 mg. There had been neither psychological nor clinical change.

HISTOLOGY OF THE ADRENAL. This differed from the other cases in having a well developed permanent cortex. The gland was both vacuolated and granular, but the vacuolation was mainly in the permanent cortex. The granular cells gave a positive Ponceau-Fuchsin reaction.

TABLE 1

BLOOD SODIUM AND POTASSIUM LEVELS IN A CASE OF VIRILISM SUBJECTED TO UNILATERAL ADRENALECTOMY (CASE 18)

Time relationship to the operation	Blood sodium in m.e. per 100 ml.	Blood potassium in m.e. per 100 ml.
9 days before	133	5·2
12 days after	130	8·0
26 days after	107	8·5
(Normal range)	139–152	4·1–4·6

Adrenocortical Obesity (Cushing's Syndrome)

Cushing's syndrome as it appears in childhood is almost always due to a tumour of the adrenal. In a review of the literature Marks et al. (1940) collected twenty-four cases, of which twenty-one were in girls. The clinical picture may differ slightly from that in adults. The obesity need not be of the 'buffalo' type but may be generalized. Hirsutism is the next most constant finding. Osteoporosis is not seen and the glucose tolerance is normal. A tendency for the cases to be of a mixed type is seen in the enlarged clitoris in eleven cases, precocious menstruation in two, and the occasional occurrence of acne. The youngest case was that described by Lightwood (1932), aged eleven weeks.

In the two cases to be described, extreme obesity was the symptom dominating the clinical picture. The only genital abnormality was a slight pubic hirsutism in one case.

Case 19. E. W., admitted at the age of 9 months, had no relevant family history. The neck was noticed to be full at five months. A month before admission she was considered to be overweight. She was happy and contented but made no attempt to crawl. Apart from the obesity, the physical examination was negative. The height was 29 in., the weight 31 lb. (Plate IIh).

Oral and intravenous tolerance curves were normal. Radiographic examination showed that secondary centres were appearing in the lower tibia, in the fibula and radius, and at the upper and lower ends of the humerus. Two approximately normal-sized ossification centres were present in the carpus.

Fatal pneumonia developed after exploratory laparotomy. At autopsy the left adrenal was found to be small. The right was replaced by a large soft mass (Plate IIIj).

HISTOLOGY. The tumour consisted of cells, oval, polyhedric, approximately spherical, occasionally of a broad fusiform or whetstone shape. The majority of the cells had a diameter of approximately 9·25 microns. The cytoplasm was wide, forming between two-thirds to three-fifths of the cell. Only in the smallest cells was the cytoplasmic rim narrow, with cytoplasm and nucleus about equal in diameter. The cytoplasm was either uniformly purplish or finely granular, but in some cells was definitely vacuolated. In some small areas the cells were highly vacuolated. The nuclei were hyperchromatic and spherical. Only occasional nucleoli were seen with the Haemalum and Eosin stain, but with Masson's trichrome and the Ponceau-Fuchsin stain definite fuchsinophil nucleoli were seen in almost all nuclei. These nucleoli varied in size. In some cells almost the whole nucleus was filled with a spherical large fuchsinophil globular mass resembling an inclusion body. In areas of necrosis numerous such fuchsinophil globules were seen. These pathologically enlarged nucleoli were not stained by the Lundrum stain which is supposed to be specific for inclusion bodies. In many cells, especially in the oval-shaped, the nucleus was eccentric. Most of the cells had one nucleus, but there were a fair number of multinucleated cells, some of the larger cells having as many as a dozen nuclei. In some of the latter there were, instead of nuclei, spherical, rod- or horse-shoe shaped bodies taking up the nuclear stain and suggesting atypical mitosis. In one area there was an arrangement of cells somewhat suggestive of those in an adrenal cortex. Numerous patchy areas of necrosis were present, and in some areas whole tumour tissue was transformed into a uniform mass staining pale blue. The vascularization of the tumour was poor and the arrangement of the cells had in some areas, where there was little dissociation of the cells, a definite epithelial pattern. The Foot stain showed scanty argentophil fibres almost entirely limited to the blood vessels and separating alveoli of the cells described above.

Case 20. M. A., aged 20 months, had no relevant family history. When six months old she was noticed to be red in the face. At eight months she became fatter. Pubic hair was noticed at nine months. She was otherwise well and good-tempered. She began to talk at thirteen months.

On admission she was found to be placid with expressionless face. She stood with support. Her height was 28 in., her weight 30 lb. (Plates IIIk, l). Apart from the generalized obesity nothing abnormal was found clinically. Oral glucose, intravenous glucose, and insulin depression curves were normal. Radiographs showed two carpal centres, a centre at the lower end of the tibia, and at the lower and upper ends of the humerus.

Laparotomy revealed a left adrenal mass which was removed. The patient died the next day with signs of pneumonia.

At autopsy the right adrenal was not definitely located. Histological examination of the perirenal tissue disclosed a gland 7·8 mm. long by 0·5 mm. broad and two adjacent nodules 1·2 by 0·3 mm. and 1·0 by 0·4 mm. The structure was that of the adult cortex. The cytoplasm was well vacuolated. The hypoplasia affected mainly the zona fasciculata and the zona reticularis. The Ponceau-Fuchsin stain was negative (Plate IIIm). The tumour had on histological examination a structure almost identical with that of the previous case.

The lobules of the thymus were small, with increase of interstitial connective tissue. Hassal's corpuscles numbered 1 to 10 per lobule and had a diameter of 26 to 70 microns.

The basophil cells of the pituitary showed the hyaline changes described by Crooke (1935), over 90 per cent. of these cells being affected to a greater or less degree. A differential count (19,500 cells) gave the following proportions: eosinophils 35·5 per cent., basophils 4·2 per cent., chromophobes 60·3 per cent. (Plate IVn and p).

DISCUSSION

The Adrenogenital Syndrome

Broster et al. (1938), who consider the presence of fuchsinophil granules in the adrenal cortex to be related to the presence of androgen, found in their study of the foetal adrenal cortex that fuchsinophil granules were present in the male foetus between the ninth and twentieth weeks of gestation and in the female from the eleventh to the fifteenth weeks. The disappearance of fuchsinophil granulation coincided with the appearance of basophil cells in the pituitary. These authors explained the occurrence of female pseudohermaphroditism on the prolongation of this masculinizing phase over the whole period of intrauterine life.

Adrenal hyperplasia in the newborn appears to be approximately equally distributed between the two sexes. The cases of Di Ruggiero and Jolly (1938), Thelander and Cholffin (1941), Butler et al.

(1939), and Skelton (1945) were all boys. Two of the four cases reported by Dijkhuizen and Behr (1940) were boys. In Thelander and Cholffin's case a sib had died with similar symptoms and was thought to be a female pseudohermaphrodite. One of the male infants in Dijkhuizen and Behr's series had a male sib who died with symptoms suggestive of adrenal hypofunction. Di Ruggiero and Jolly's boy had had three sibs, all boys, who died respectively at the age of thirty-two, forty, and sixty-one days with chronic vomiting and failure to gain weight attributed to various causes. One of our pseudohermaphrodites had had a sib reported as being a hermaphrodite and who had died of 'pyloric stenosis.' In our series there were five of each sex. This apparently equal distribution between the sexes, together with the comparatively frequent reports of familial occurrence, suggests that there is an inherited factor determining the hyperplasia of the suprarenals and that this factor is not sex linked.

The elaboration of the abnormal masculinizing hormone is apparently associated with a failure to produce the more essential 'salt and water' hormone. This has been likened to acute Addison's disease both on account of the blood electrolyte picture (Butler et al., 1939) and because of the results of treatment with salt and desoxycorticosterone (Thelander and Cholffin, 1941). Pigmentation of the skin actually occurred in Butler's case. In early infancy the hyperplasia of the suprarenal glands is often associated with a fairly characteristic clinical syndrome. This consists of failure to thrive, persistent severe vomiting which may be projectile and suggestive of pyloric stenosis (two of our cases), faeculent and suggesting intestinal obstruction (Dijkhuizen and Behr, 1940). Attacks of acute circulatory failure resembling shock are frequent and were stressed by Harris (1946) and other authors. Four of our male cases showed this liability to sudden collapse. The rapid respiration in one of the male cases recalled the syndrome of acute adrenal insufficiency in the newborn due to haemorrhage into the gland, which Goldzieher and Gordon (1932) referred to as 'pseudopneumonia.'

The diagnosis is not difficult provided the possibility is considered. It may be made on the blood levels of sodium, potassium, and chloride, or on the dramatic response to salt and hormone therapy. In a neonate with hypospadias and absence of testes in the scrotum, attacks of acute circulatory failure should raise suspicions. In male babies the lead is less obvious. Acute collapse is not uncommon in a poorly infant. In two of the authors' cases a special note was made of the persistence of urinary chloride in spite of continued vomiting. This may be considered to be an excessive urinary chloride excretion comparable to that in Addison's disease. With the growing appreciation of the importance of the rôle of salts in tissue fluids, the urine is likely to be tested as a routine for chlorides more frequently in the future than it has been in the past. It is suggested that, in an obscure case of intractable vomiting, if the chlorides do not virtually disappear from the urine, adrenal cortical hypofunction should be considered to be a possibility. In the neonatal period this may occur not only in cortical hyperplasia but as a temporary phenomenon, when it is presumably due to birth trauma (Jaudon, 1946).

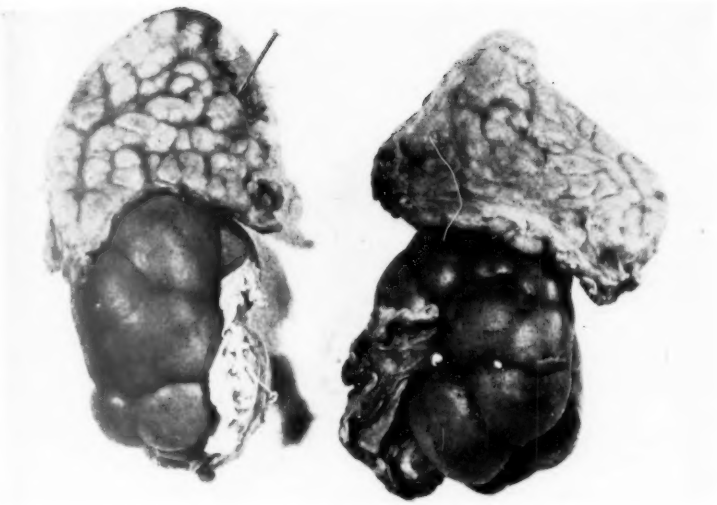
There is ample experimental evidence that the adrenal cortical hormones are concerned with the regulation of carbohydrate metabolism. Adrenalectomy leads to a mobilization of the glycogen in the tissues, and the liver becomes practically glycogen free. Administration of cortical extract, on the other hand, increases the liver glycogen. In vitro, glycogenolysis is inhibited by cortical extract, hypoglycaemia being produced notwithstanding large glycogen depots. It would appear suggestive that in case 15, with glycogen storage disease, the cortical hyperplasia was associated with an increased production of those cortical hormones which, like corticosterone, have an oxygen atom at C_{11}.

As far as is known the association of adrenal hyperplasia with glycogen storage disease has not been hitherto described, though the possibility was suggested by Long (1942). In fact Ellis and Payne (1936) in a review of the literature of von Gierke's disease, found three cases with adrenal hypoplasia but, in the majority of cases, the adrenal was normal. It is, of course, purely hypothetical to draw conclusions from a single case, but in future more attention should be paid to the glycogen content of the liver in suprarenal cortical hyperplasia.

It is a striking fact that, although interrenal pseudohermaphrodites surviving for several years show invariably evidence of precocious growth and ossification, these children are normal in size at birth. In none of the reported cases was the baby stated to be particularly big at birth. We have paid special attention to this point. All our cases in the neonatal period were normal in size and in none of the five cases in which x-ray examination was carried out was there any evidence of precocious ossification.

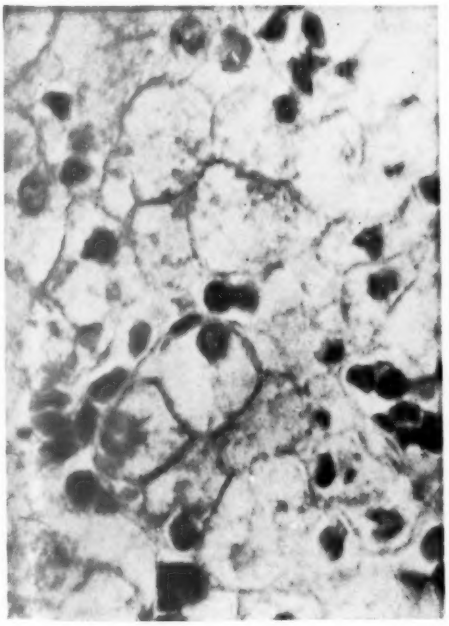
There are a number of possibilities which might explain the postnatal onset of the somatic as distinct from the sexual disturbance. Firstly, the suprarenal hormones are not responsible for growth and ossification directly, but act through changes in such glands with internal secretion as are known to have an influence on growth and ossification, such as the pituitary and the gonads. The latter, however, have shown no changes in our cases. The pituitary has to be further investigated, but the fact that hyperfunction of eosinophil cells in the anterior pituitary lobe is associated with giantism and delayed union of epiphyses, while in macrogenitosomia praecox the rapid growth leads to a precocious ossification of the epiphyseal lines and results finally in a dwarfed stature, makes such an explanation improbable.

Secondly, there are different hormones in the suprarenal cortex influencing the development of the

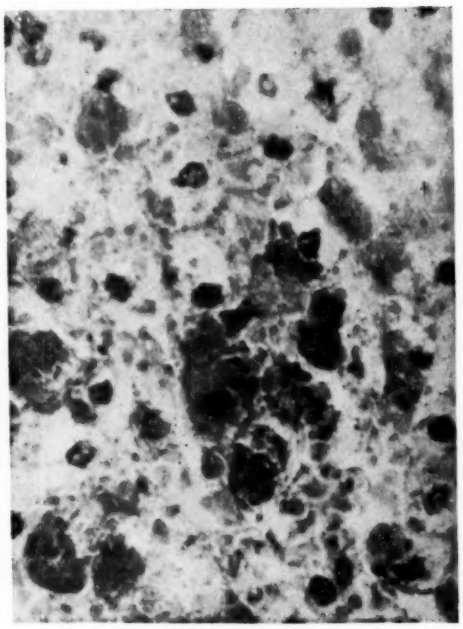


(a) top left—Enlarged adrenal glands due to hyperplasia.

(d) right—Macrogenitosomia praecox in a boy due to adrenal hyperplasia (case 16).

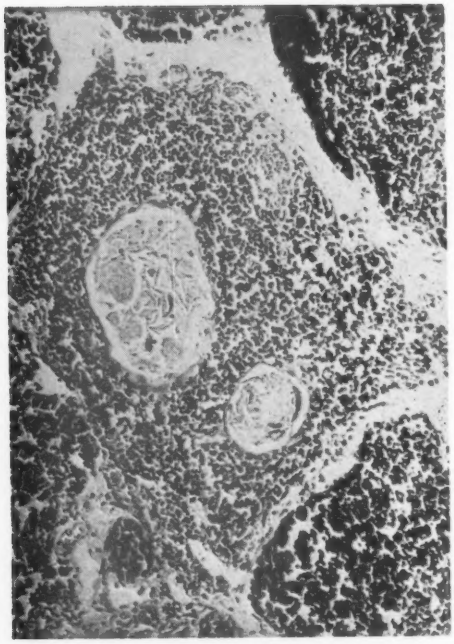


(b) lower left—Liver of case 15, with glycogen storage disease, showing the characteristic plant like appearance of the swollen liver cells. Haematoxylin and Eosin.

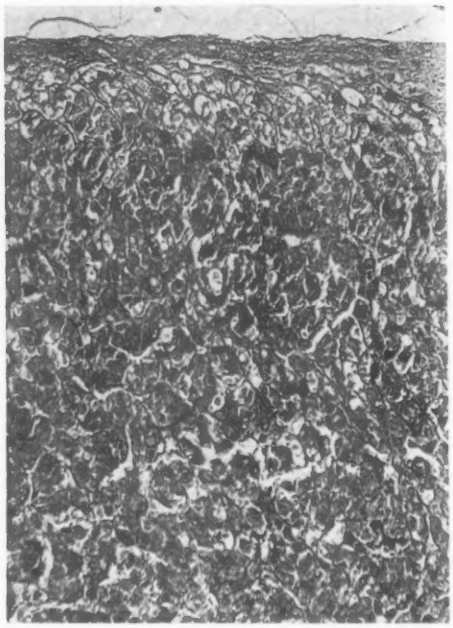


(c) lower right—Liver of case 15, with glycogen storage disease, showing liver cells filled with glycogen. Best's Carmine stain.

PLATE I



(e)—Thymus from case 16, macrogenitosomia praecox in a boy, showing enlarged Hassal's corpuscles. Haematoxylin and Eosin.

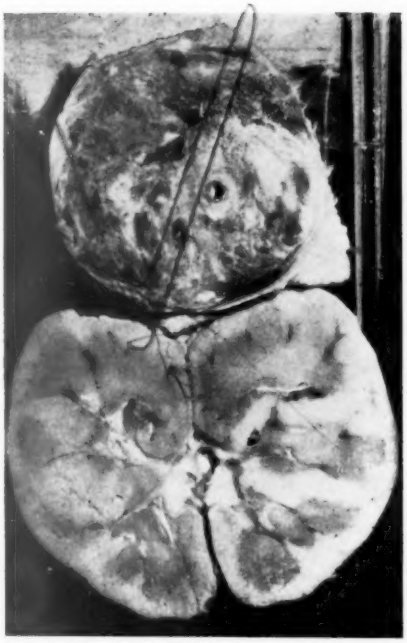


(f)—Low-power microphotograph of the adrenal cortex in pseudohermaphroditism (case 17), showing predominance of a transient cortex composed of granular fuchsinophil cells. Ponceau-Fuchsin stain.

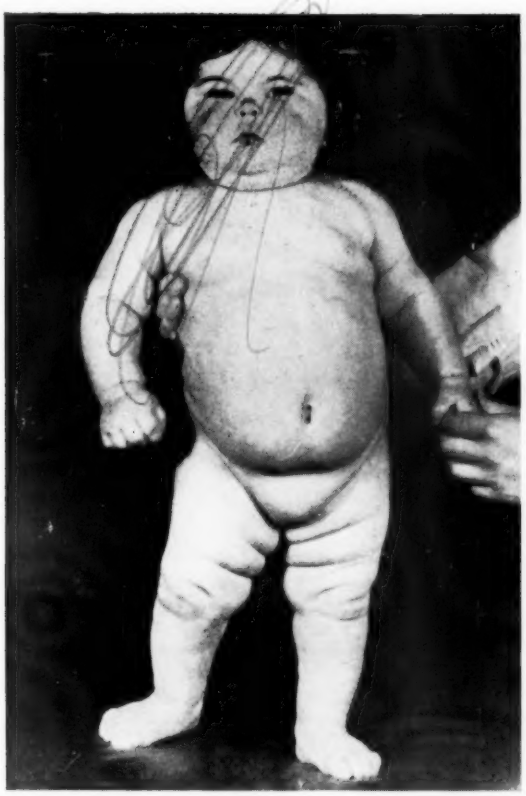
(g)—Masculine configuration in a female pseudohermaphrodite (case 18).

(h)—Generalized obesity in Cushing's syndrome (case 19).

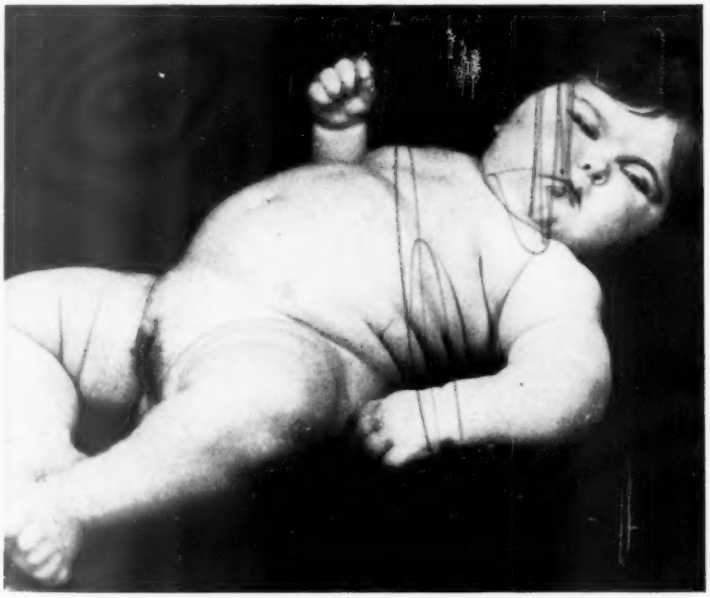
PLATE II



(j) top left—Carcinoma of adrenal causing Cushing's syndrome (case 19).



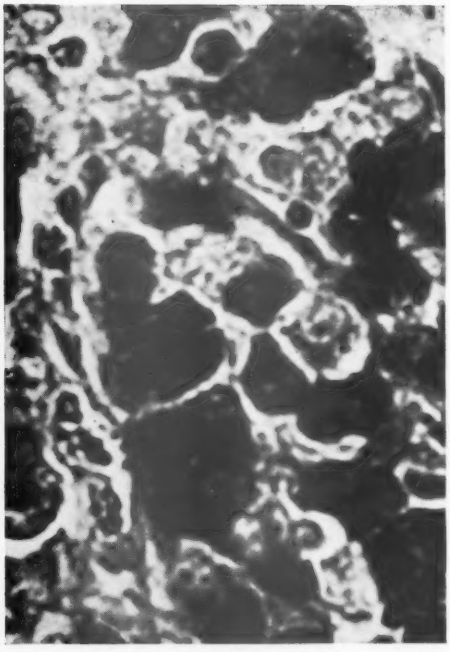
(k) top right—Plethoric facies and generalized obesity in Cushing's syndrome (case 20).



(l)—Hirsutism in Cushing's syndrome (case 20).

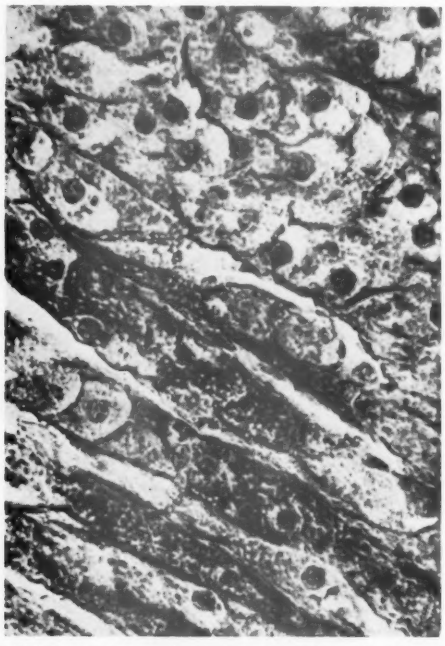
(m)—The contralateral gland to an adrenal carcinoma causing Cushing's syndrome (case 20), consisting solely of an atrophic adult cortex made up of vacuolated cells. Haematoxylin and Eosin.

PLATE III

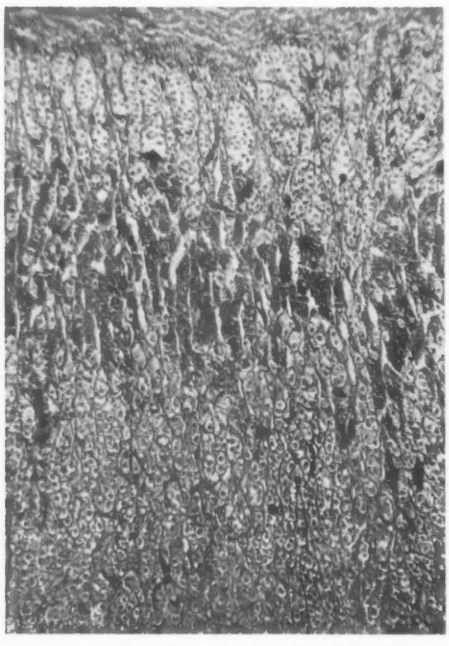


(n)—Normal pituitary, showing groups of basophil cells packed with dark blue granules. High power. Mann's methylene blue Eosin.

(p)—Pituitary basophil cells in Cushing's syndrome (case 20). The basophilic granulation has been largely replaced by a pale grey hyaline cytoplasm. Oil immersion. Mann's methylene blue Eosin.



(q)—High-power microphotograph of the adrenal cortex to show granular and hyaline cytoplasm existing contiguously. Ponceau-Fuchsin stain.



(r)—Permanent cortex in a pseudohermaphrodite (case 18), showing a band of granular fuchsinophilic cystoplasm (dark) in the peripheral part of the zona fasciculata. Ponceau-Fuchsin stain.

PLATE IV

secondary sexual characters on the one hand and bone growth on the other, the latter being formed in later childhood. Although there is no experimental evidence for the existence of two such hormones, Venning and Kazmin (1946) found that the proportions of the individual hormones produced by the adrenal cortex varied with the age of the child.

Thirdly, the action of the suprarenal hormones depends on the developmental stage of the effector organs.

Fourthly, some maternal hormones may counteract the growth-promoting effect of the suprarenal hormones and their action may still manifest itself for some time after birth.

Fifthly, the histological work of von Lucadou (1938) strongly suggested that the suprarenal cortex and medulla, although phylogenetically and ontogenetically different organs, form a functional entity in higher mammals. Some of the suprarenal hormones appear to be secreted through glandular lumina into the medulla, and the medullary secretion may modify the action of the cortical hormones. The adrenal medulla, being only a small part of the entire organ in the newborn, and increasing in size not only absolutely but relatively, may thus be responsible for the different effects of cortical hormones in foetal and early neonatal life on the one hand, and later childhood on the other.

In the authors' opinion there is at present insufficient evidence to give preference to any of these hypotheses.

The adrenogenital syndrome appearing in later childhood may be due to either hypertrophy or to tumour, usually carcinoma, of the adrenal. These cases, however, occur predominantly in girls. Goldstein et al. (1946) collected from the literature fifty-four cases of carcinoma of the adrenal cortex which showed the adrenogenital syndrome. Of these, twelve were boys. The disproportion between the sexes becomes even more pronounced when cases of adrenal cortical hyperplasia are considered, a condition which occurs almost exclusively in girls. Up to the present there have been only two cases reported in boys where the cause of the macrogenitosomia praecox was proved to be due to a hyperplasia (Wilkins et al., 1940; Thelander, 1946). It is likely that Thelander's case would not have survived beyond infancy if it had not been treated with salt and desoxycorticosterone. The sex difference was so striking as to make Thelander and Cholffin (1941) raise the question whether these cases of female pseudohermaphrodites, with marked hypertrophy of the 'androgenic' zone but without marked symptoms of cortical insufficiency, belonged to the same etiological group.

Another possible explanation may lie in the effect of synergistic and antagonistic hormones on cortical function causing a higher survival rate among the females with cortical hyperplasia than among the males. Testosterone has been shown to inhibit adrenal cortical function (Albright, 1942). Oestrone not only causes adrenal hypertrophy, but pregnancy and oestrus favour the survival of adrenalectomized animals. Further, pituitary implants prolong the life of adrenalectomized female animals but not of the adrenalectomized male or of the adrenalectomized female castrate (Goldzieher, 1945a). If the male infant were to produce testosterone and the female infant oestrone, even in small amounts, the effect of these hormones might be such as to tip the balance in favour of the survival of the female.

The Adrenocortical Syndrome

Our two cases of suprarenal cortical carcinoma support the conception of the existence of tumours with different hormonal action. Both showed an extreme obesity, but neither masculinization nor precocious growth. Some of the cortical tumours, however, in the literature appear to have produced both 17-ketosteroids, causing masculinization, and metabolic hormones causing obesity. This may be due to a primary mixed hormone production, or the elevated 17-ketosteroid formation may represent a compensatory increase in an attempt to counteract the pathologically elevated 'S' hormone production, as has been suggested for Cushing's syndrome in the adult by Albright (1942).

Sudden Death in Adrenocortical and Adrenogenital Dysfunction

In cases of Cushing's syndrome due to an adrenal cortical tumour, Cahill et al. (1942) stressed the liability of the function of the contralateral gland to be suppressed, resulting in the danger of sudden death from acute adrenal insufficiency if the tumour were removed. This contrasted with the bilateral adrenal hyperplasia seen in cases of virilism in adult women.

That a tumour can not only cause a suppression of function, but that it can be associated with a contralateral atrophy of the adrenal is well seen in case 20, where the opposite gland measured 8·0 mm. by 0·5 mm. and was not found on naked-eye examination, although the perirenal fat was thoroughly dissected and examined. While it is agreed that in virilism in adult women portions of the adrenals can be removed safely and with amelioration of symptoms (Broster, 1946), the possibility exists that, as both glands are being stimulated to form androgens, they may fail to produce adequate amounts of the more vital hormones. This is clearly so in the infantile cases of hyperplasia. It might account for the death in case 17, the six-year-old pseudohermaphrodite for whose rapid decease no other adequate cause was found. In considering case 16, the male macrogenitosomia praecox who died twelve hours after a left adrenalectomy, the recent history of diarrhoea may have been an indication of an incipient metabolic breakdown. This assumption finds further

support from the condition at autopsy of the thymus, which was fleshy and succulent, weighing 32 g.; and the mesenteric glands and Peyer's patches, enlarged and hypertrophied, were suggestive of a diminished function of the adrenal (Goldzieher, 1945b). Thelander's case (1946) of macrogenitosomia praecox at the age of seven years, was killed by measles within twenty-four hours in spite of a previously adequate salt and desoxycorticosterone therapy. A possible cause for the stormy convalescence of case 18 after left adrenalectomy is shown in the serum sodium and potassium values, the latter figures, in particular, suggesting a cortical hypofunction.

The eventuality of acute adrenal failure should, therefore, be kept in mind when dealing with any case of possible cortical hyperplasia in children, although the danger is likely to be more pronounced in cases of suprarenal neoplasm with obesity.

Histology of the Adrenal Cortex in Hyperplasia

In the newborn period the appearance of the glands was very variable. In places there was a well marked permanent cortex. At other sites in the same gland the tissues had the structure of the transient cortex except for a narrow band of zona glomerulosa. The cytoplasm was equally variable, in parts granular, in others vacuolated (Plate IVq). The transient cortex tended to be the more granular, the permanent cortex the more vacuolated, but on the whole we had the impression that in the cases with adrenal cortical hyperplasia the cell types with the cytoplasm showing fine granules in haemalum and eosin stains was prevalent, while cells with a vacuolated cytoplasm, especially those with large vacuoles, formed only a small part of the cortical tissue. The Ponceau-Fuchsin stain was often negative. This may be due to the fact that most of our material was obtained at necropsy. The influence of post-mortem changes on the result of the Ponceau-Fuchsin stain was obvious in case 16, where one adrenal was obtained at operation, the other after death. Broster et al. (1938) pointed out that the presence of fuchsinophil granulation was only an indication of androgenic material present at the time of fixation and gave no index of the previous activity of the gland. Further, Vogt (1943) found that the amount of cortical hormone continually being excreted was enormous when compared with the quantity which could be extracted from the gland tissue. Thus, either the methods of extraction were inadequate or the adrenal cortex did not store its principles in active form. In the latter event a discharge of hormone without new formation, even for a very short time after death, would thus explain the frequent occurrence of negative Ponceau-Fuchsin staining in autopsy material. When positive the stain was more noticeable in the transient cortex.

Where there were nodules of adenomatous hyperplasia the structure might be that of either transient or permanent cortex. In the latter case there was not the usual zonal demarcation. In the hydrops foetalis the vacuolation of the cortical cells, particularly the transient cortex, was gross.

In the adrenogenital syndrome in older children the cortex was mainly transient in cases 16 and 17, and Vines' Ponceau-Fuchsin reaction was positive. In the older case of virilism (case 18), there was a well developed permanent cortex. The cells were both vacuolated and granular but the vacuolation was mainly in the permanent cortex. Granular cytoplasm in both types of cortex gave a positive Ponceau-Fuchsin stain (Plate IVr).

These findings, and those in the case of Cushing's syndrome, are in agreement with the observation of Broster et al. (1938) that the fuchsinophil material is not limited to a zone of tissue in the juxtamedullary region which Grollman (1936) considered to be the androgenic zone. The fuchsinophil material, when present, occurred only in those cells showing acidophil granules with haemalum and eosin. Vacuolated cells, considered by Cahill et al. (1942) to be typical of the Cushing type of syndrome, did not show fuchsinophil granules.

Summarizing all our histological findings, including a series of normal newborn adrenals examined for the presence of Sudanophil material, for anisotropic lipoids, and by the Ponceau-Fuchsin stain, it appears that the transient type of cortex is more concerned with the formation of androgenic hormones than is the permanent cortex. There is some relationship between the presence of fuchsinophil granules and androgenic function, but the latter is not limited to a particular type of cortical tissue nor to cells with a definite morphology.

The Pituitary in Relation to the Adrenogenital and Adrenocortical Syndromes

Since Cushing (1932) described the association of a basophil adenoma of the pituitary with the syndrome to which subsequently his name was attached, the latter condition has also been found in conjunction with both tumours and hyperplasia of the adrenal glands. The clinical picture of Cushing's syndrome is so clear cut that there is presumably some common factor in the etiology. As patients with cancer of the adrenals and Cushing's syndrome are probably suffering primarily from an hyperadrenocorticism of some kind, then, on the assumption of a uniform pathological basis, all patients with Cushing's syndrome are suffering from hyperadrenocorticism (Albright, 1942). In these cases the only constant finding in the pituitary is a hyalinization of the cytoplasm of the basophil cells, described by Crooke (1935). Kepler (1945) considered these changes to be secondary to the adrenal hyperplasia, being in the nature of the effects of depression of function of the basophil cells which were considered to secrete the adrenotropic agent. Marks et al. (1940), in a review of the literature of adrenocortical obesity in children, quoted one case

as having hyaline changes in the basophil cells of the pituitary, though in their own case there was a slight increase in the number of acidophil as compared with the basophil cells. These hyaline changes were well shown in case 20 (Plate IVp).

It is of particular interest in this connexion that partial hypophysectomy causes a hyperplasia of the adrenal cortex in rats, associated with an increased amount of body fat and at the same time changes in the cells of the pituitary remnants which are apparently identical with those described by Crooke and observed in case 20 (Reiss et al., 1937). Total hypophysectomy, on the other hand, causes an atrophy of the suprarenal cortex involving mainly the inner zone of the cortex (Crooke and Gilmour, 1938; Swann, 1940). The bulk of evidence appears to support the idea that the pituitary changes are secondary to the suprarenal hyperplasia. The frequent dogmatic statement that the basophil cells of the pituitary anterior lobe are the site of the formation of adrenocorticotropic hormones, appears to be not fully justified, as adrenal hyperplasia was also described in acromegaly by Fischer (1926).

There is no clear relationship between the adrenogenital syndrome and changes in the cells of the anterior pituitary. Wilkins et al. (1940), in their case of macrogenitosomia praecox in a male associated with cortical hyperplasia, reported a relative preponderance of basophil cells. Reilly et al. (1939), reviewing forty cases of ' pseudo-sexual precocity ' in preadolescent girls, stated that the pituitary was alleged to be normal in two cases, there was an eosinophil adenoma once, a colloid cyst and atrophy once, cystic hypoplasia once. These authors did not, however, make a clear distinction between the adrenogenital and the adrenocortical syndromes, possibly because the clinical picture is so often mixed.

Where the material was available, differential cell counts were made after the method of Rasmussen and Herrick (1922). The stain used was Mann's methylene blue eosin.

The only modification was in the number of fields counted. Rasmussen examined every fifth field in every fifth row, in this way counting between 10-30,000 cells per gland. In order to count this number of cells in the smaller glands it may be necessary to count every fourth field in every fourth row or even every third field in every third row.

The results of the differential counts are given in table 2. It is felt the results are too few to draw any conclusions, as these figures are within the range of normal for adults (Rasmussen, 1929, 1933).

Thymus

The thymus undergoes rapid involution in any condition where there has been a call on the adrenal hormones. Conversely the thymus shows hyperplasia in the case of chronic disease or hypoplasia of the adrenals. The atrophy of the thymus frequently found in cases of interrenal pseudohermaphroditism was by several authors considered to be a result of adrenal cortical hyperplasia, being the antithesis of thymic persistence in Addison's disease. We feel that such a conclusion is not supported by facts. Our infantile cases showed marked atrophy of the thymus in five out of ten cases, but that is a common finding in infants after prolonged disease.

Hornowski (1926) found in newborn infants that a prevalence of epithelial elements of the thymus was associated with an inhibition of suprarenal development, while a prevalence of lymphatic elements was associated with a normal development of the suprarenals. It may, therefore, be of some significance that in our cases 6 and 16 there were enlarged Hassal bodies.

Diagnosis of the Adrenogenital and Adrenocortical Syndromes

The diagnosis of the adrenocortical syndrome has to be made from other forms of obesity, and has been discussed by Marks et al. (1940). The tumour may be difficult to palpate because of the obesity. Perirenal insufflation of air has been successfully used to delineate the mass.

The adrenogenital syndrome has to be distinguished in the male from pineal, midbrain and hypothalamic, testicular, and thymic tumours; in the female from midbrain, hypothalamic and thymic tumours, and arrhenoblastoma and granulosa cell tumours of the ovary. The differential diagnosis of

TABLE 2
DIFFERENTIAL CELL COUNTS OF THE PITUITARY

Case No.	Condition	Eosinophils per cent.	Basophils per cent.	Chromophobes per cent.	Total cells counted
—	Control	14·4	10·0	75·6	14,837
—	,,	14·0	2·7	83·3	22,636
4	Female pseudohermaphrodite	25·7	18·8	55·5	11,720
6	Male hyperplasia	13·3	9·1	77·6	21,304
15	S.B. with glycogen storage disease	15·3	4·8	79·9	9,792
16	Male macrogenitosomia	50·0	2·3	47·7	17,249
20	Cushing's syndrome	35·5	4·2	60·3	19,532

these conditions has been considered by Goldstein et al. (1946), Kepler and Keating (1941), Goldzieher (1945c), and Soffer (1946).

Of help in the confirmation of the diagnosis in the adrenogenital syndrome is the increase of the urinary 17-ketosteroids, premature ossification as shown by radiograph, and the examination of biopsy material. For reasons already discussed, the Ponceau-Fuchsin stain seems to be more reliable with specimens taken at operation than at autopsy.

Although the adrenogenital syndrome shows frequently such a characteristic clinical entity that the diagnosis presents no difficulty, cases are occasionally encountered in which adrenal hyperplasia can be neither diagnosed nor definitely excluded. This is well illustrated by one of our cases, a girl aged three years, not previously quoted, where the clinical signs were an enlargement of the clitoris since the age of two years, precocious ossification without increased rate of growth, hirsutism, or increased urinary output of 17-ketosteroids, and without any evidence of intracranial disease.

SUMMARY

From a review of the case material of the Birmingham Children's Hospital during the last ten years, ten cases of adrenal hyperplasia in the newborn with symptoms of adrenal cortical hypofunction are described, and the symptomatology and the diagnosis discussed. The estimation of the urinary chloride as a diagnostic aid is emphasized. The differences in the clinical picture between the adrenogenital syndromes in the newborn and in older children are pointed out.

Five further cases of adrenal hyperplasia in the newborn are described, two in haemolytic disease of the newborn, two with exomphalos, and one stillborn with glycogen storage disease.

The adrenogenital syndrome in older children is represented by three cases, all due to hyperplasia. One boy presented the typical picture of macrogenitosomia praecox. The two girls were both pseudohermaphrodites.

Two girls with adrenocortical obesity or Cushing's syndrome due to adrenal cortical carcinoma are described.

The liability of the above cases to sudden death is stressed.

An attempt is made to correlate the two syndromes with histological changes in the adrenal cortex. Although the proportion of transient to permanent cortex was very variable in adrenal hyperplasia in the newborn, the transient cortex predominated in the adrenogenital syndrome in older children but was completely absent in the atrophic contralateral adrenal to the carcinoma in Cushing's syndrome.

Fuchsinophil material, when present, was predominantly in the transient cortex and was probably concerned with the production of androgens, whereas the cytoplasm of the permanent cortex was mainly vacuolated and presumably concerned with adrenocortical hormone production.

The relationship of the pituitary and thymus to the interrenal syndrome is discussed.

Our thanks are due to the Honorary Staff of the Children's Hospital, Birmingham, for permission to publish their cases, to Mr. A. R. Detheridge for the microscopical sections, and to Mr. J. Gregory Williamson for the photographs.

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URINALYSIS IN DEHYDRATION FEVER

BY

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Introduction

In the course of carrying out a series of observations on renal output and the composition of the urine in the newborn period, two cases of dehydration fever were observed. The observations recorded in these two cases deviate so far from the normal, Thomson (1944), that their separate recording is desirable.

Case Records

Baby M.—Baby M. was born spontaneously at 1.45 p.m. and weighed 9 lb. 2½ oz. It was the first baby of a young mother aged 22 years. The weight curve was within normal limits and the number of stools passed was not excessive. Under test feeding conditions the baby was put three times to the breast in the first twenty-four hours, but it obtained no measurable amount of fluid. During this period two separate half-ounce feeds of 5 per cent. glucose in normal saline were given at 12 midnight and 6 a.m. Subsequently the baby was put to the breast at three-hourly intervals, always under test feeding conditions, and was given no further extra fluids except one ounce of sterile water at 3 p.m. during its fourth twenty-four-hour period. A record of the test feeds was kept (table 1).

TABLE 1

BABY M. TEST FEEDS IN OUNCES

Day	1	2	3	4	5	6	7	8	9
3 p.m.	—	Nil	Nil	1½	1½	1½	2	1½	2½
6 p.m.	—	Nil	Nil	½	3	1½	2½	3½	2½
10 p.m.	Nil	Nil	Nil	1½	2½	1½	1½	2½	2½
12 midn't 6 a.m.	½ g. ½ g.	— Nil	— ½	— ½	— 3½	— 2½	— 1½	— 2½	— 2½
9 a.m.	Nil	½	Nil	1½	1½	1½	2	1½	2½
12 noon	Nil	Nil	Nil	1½	2½	1½	3½	5½	—
Total	1	½	½	6½	14½	10½	12½	17	13½+

Using an apparatus described in a previous article, Thomson (1944), the output of urine and time of voiding were continuously recorded. The daily total volume of urine was examined as to its specific gravity, urea, and chloride concentration. These results are shown in tables 2 and 3.

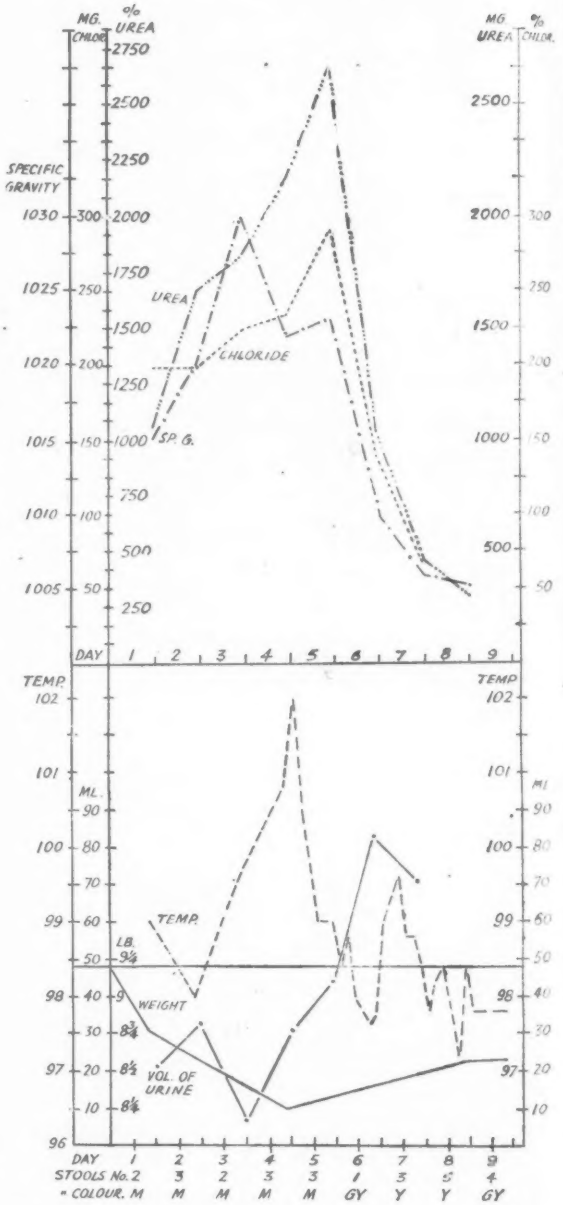

FIG. 1.—Baby M. To show weight, temperature, volume of urine output, specific gravity, and urea and chloride concentration of urine.

TABLE 2

BABY M. TIMES OF VOIDING AND VOLUME OF URINE PASSED

Day										Totals
1	a.m. 8.50 ml. 9·5	10.50 11·5								21
2	p.m. 2.30 ml. 7·5	6.50 4	a.m. 3.50 6	8 12	11 1	p.m. 12.30 2				32·5
3	a.m. 5.30 ml. 1·5	p.m. 1.30 4	1.35 1·5							7
4	p.m. 5.30 ml. 7	8.30 4	10.15 2	11.30 1·5	a.m. 1.30 2·5	5.30 2	7.30 1	7.50 5	p.m. 12.45 6	31
5	p.m. 4 ml. 3	7 5	8.30 36							44
6	p.m. 2.30 ml. 8	8.30 9	9 5	1 3	1.35 36	1.45 22				83
7	p.m. 4 ml. 39	5 17	a.m. 9 15							71
8	p.m. 4 ml. 7	5 28								

Towards the end of the third twenty-four-hour period, and coinciding with a diminution of the urinary output, the baby became irritable and restless, crying frequently and lustily, having parched lips and tongue and a dry hot skin. A temperature of 99·6° F. was recorded, and a four-hourly chart was kept until the pyrexia ceased (fig. 1).

The infant was discharged clinically well and fully breast fed on its tenth day, weighing 8 lb. 9 oz.

Baby B.—Baby B. was born at 4.35 p.m. and weighed 6 lb. 7 oz. It was the spontaneously delivered baby of a 20-year-old primpara. The weight curve approximated to the normal, while the number of stools passed was not excessive, although eight were recorded on the seventh day of life. The baby was put to the breast five times in the first twenty-four hours but obtained no measurable quantity of fluid other than ½ oz. at the 3 p.m. feed. In this instance also regular three-hourly test feeding was carried out and the results are shown in table 4. No fluid other than that obtained at the breast was given.

TABLE 4

BABY B. TEST FEEDS IN OUNCES

Day	1	2	3	4	5	6	7	8	9
6 p.m.	—	Nil	Nil	1	1½	1½	3	1½	2
10 p.m.	Nil	Nil	½	1½	2	2½	2½	2½	3½
6 a.m.	Nil	½	1	1½	2½	3	1½	2½	3
9 a.m.	Nil	Nil	1	1½	1½	3½	3	2½	3
12 noon	Nil	½	½	1½	1½	1½	1½	2	4½
3 p.m.	½	½	1½	1½	2½	2½	2½	2½	3
Total	½	½	4½	8½	11½	14½	14	14½	18½

As in the previous instance, records were kept of the urinary output and times of voiding, table 5, while the results of urinalysis are given in table 3.

TABLE 3

DAILY VOLUME OF URINE WITH SPECIFIC GRAVITY, CONCENTRATION OF UREA, AND CHLORIDES COMPARED WITH AVERAGE FIGURES. THOMSON (1944)

	Daily output of urine			Specific gravity			Urea concentration mg. %			Chloride concentration mg. %		
Day	Average normal ml.	Baby M.	Baby B.	Average	Baby M.	Baby B.	Average	Baby M.	Baby B.	Average	Baby M.	Baby B.
1	19·5	21	Nil	1012·2	1015	Nil	670	1060	Nil	250	198	Nil
2	20·6	32½	3	1014·6	1020	—	956	1670	600	194	198	410
3	36	7	3½	1013	1030	—	690	1820	1710	129	222	139
4	64·8	31	8½	1010	1022	1025	497	2160	1990	89	234	151
5	103·3	44	31	1009	1023	1013	324	2660	1610	146	292	187
6	124·5	83	59	1009·2	1010	1008	286	1030	860	153	139	91
7	146·6	71	106	1008·8	1006	1006	272	470	470	163	67	79
8	151	—	—	1008	1005	—	282	300	—	142	—	—
9	175·4	—	—	1007·8	—	—	250	—	—	122	—	—

As in the case of the first baby, pyrexia with the accompanying clinical signs of dehydration fever became manifest towards the end of the third twenty-four-hour period. A temperature of 99·8° F. was then recorded, and a four-hourly chart was kept until the baby was eight days old and all pyrexia had ceased (fig. 2).

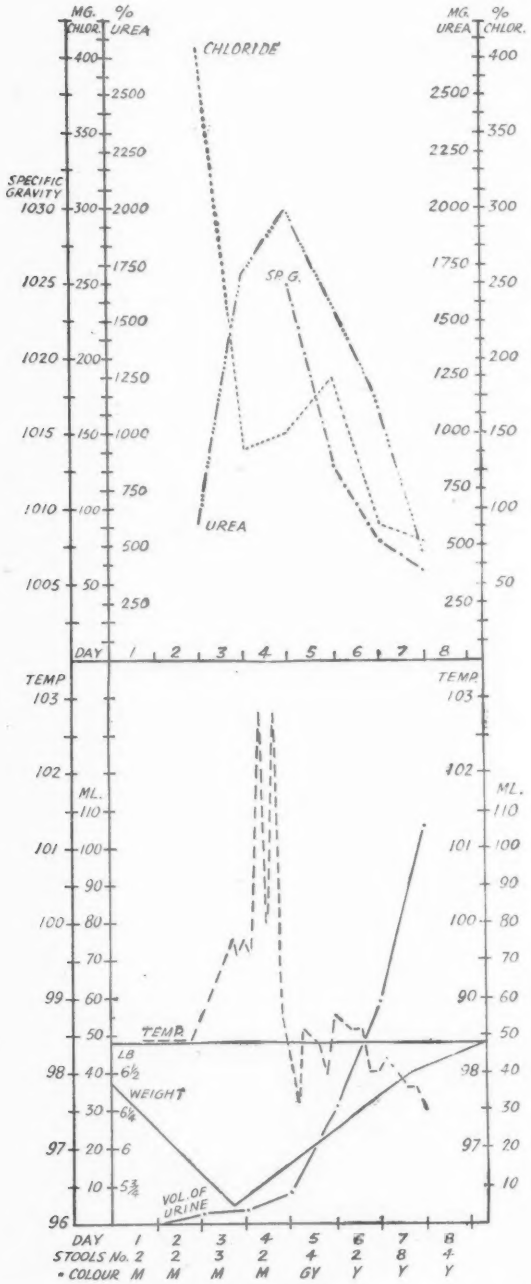

FIG. 2.—Baby B. To show weight, temperature, volume of urine output, specific gravity, and urea and chloride concentration of urine.

The infant was discharged fully breast fed on its thirteenth day when it was 6½ oz. over its birth weight.

Discussion

Since Holt (1895) first described this condition the results of investigations by various workers have gradually narrowed down the probable cause to one of dehydration. That dehydration can produce pyrexia has been proven experimentally by Balcar et al. (1919). The literature was surveyed by

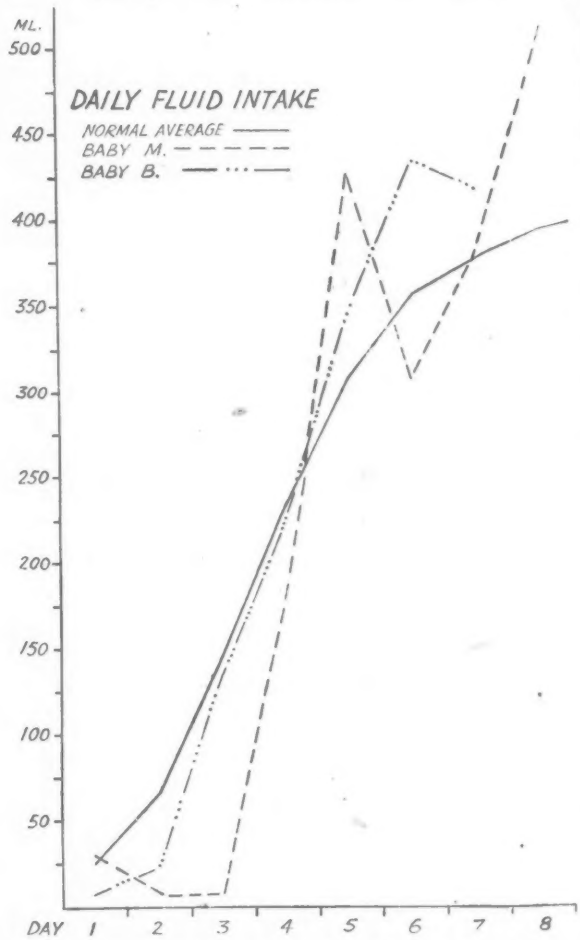

FIG. 3.—Daily fluid intake, babies M. and B. compared with normal average.

Grulee and Bonar (1921), who demonstrated that there is no relationship between the amount of the babies' weight loss and the incidence of pyrexia, nor between the amount of the fluid intake and the pyrexia.

In his investigation into the serum protein concentration in the newborn, Bakwin (1922) has shown that the occurrence of dehydration fever is related to an increasing concentration of serum protein which coincides with the so-called physiological weight loss. He has also demonstrated that the incidence of the fever is not related to the amount

of the weight loss, and suggested that the level of the body water reserve at birth is an important determining factor.

In a later publication, Bakwin et al. (1922) demonstrate that the pyrexia is readily relieved by giving 30 to 40 ml. water per kilo of body weight by mouth. Examination of the urine in such cases of pyrexia in the neonatal period might well be

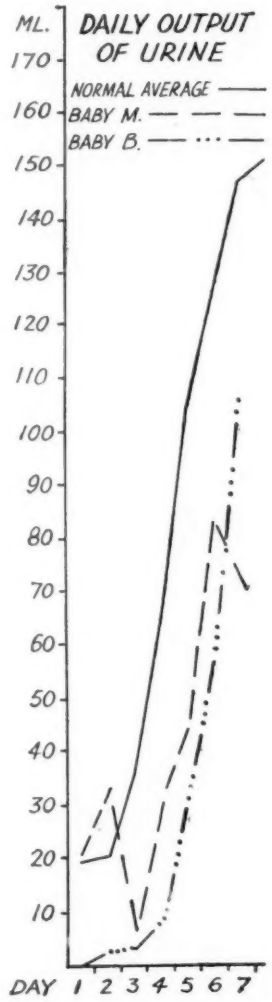

FIG. 4.—Daily output of urine, babies M. and B. compared with normal average.

expected to suggest some confirmation of Bakwin's thesis that the fever is the result of dehydration. A survey of the literature shows, however, that no investigator has published any such work to date. Grulee and Bonar (1921) state that no attempt was made to conduct a urinalysis. Because of this omission it is felt that the results of urinalysis in these two cases may be of some value.

The daily output of urine in both cases is below average, Table 3, but as the daily fluid intake is also

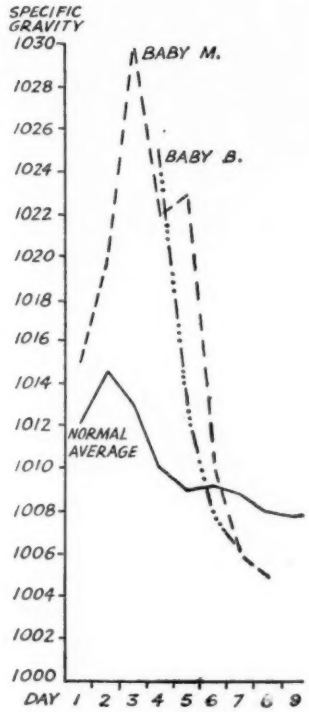

FIG. 5.—Specific gravity, babies M. and B. compared with normal average.

TABLE 5

BABY B. TIMES OF VOIDING AND VOLUME OF URINE PASSED

Day									Totals
1	Nil								Nil
2	p.m. 11.15	a.m. 9							
	ml. 1·5	1·5							3
3	Time uncertain								
	ml. 3·5								3·5
4	a.m. 10	p.m. 1							
	ml. 7·5	1							8·5
5	p.m. 5.50	1.20							
	ml. 3	28							31
6	p.m. 7.30	11.30	a.m. 12.30	2.15	11.50	p.m. 3	3.1	4.10	
	ml. 12	6	4	7	7	5	12	6	59
7	p.m. 5	6.50	8.15	8.30	8.45	11.45	a.m. 12.30	3.45	
	ml. 7	11	6	9	4	3	4	5.5	
	a.m. 7	10	10.15	11.25	p.m. 12.40	12.50	1.30	3.10	
	ml. 8·5	5	4	7	2	4	7	13	
	p.m. 3.50								
	ml. 6								106

below average until the fifth day, this is not surprising (fig. 3).

The relationship between the intake of fluid and the output of urine is such that a negative water balance is obvious in the case of Baby M. during the first three days of life. In the case of Baby B.

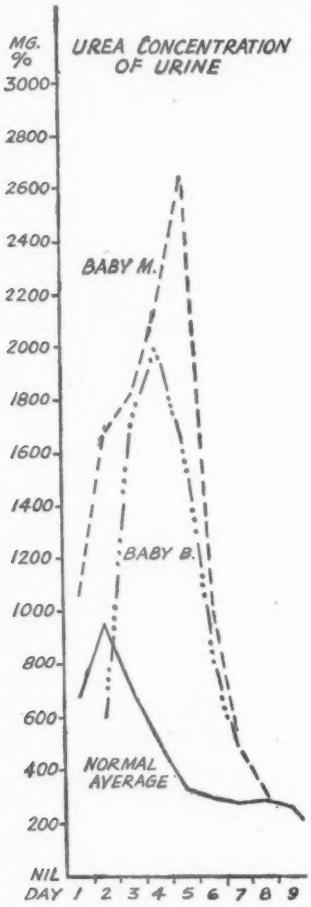

FIG. 6.—Urea concentration of urine, babies M. and B. compared with normal average.

the absence of the passage of urine during the first twenty-four-hour period is not to be considered abnormal, since it is not uncommon for a normal newborn infant to pass urine for the first time during its second twenty-four-hour period: while, rarely, the event may be delayed till the third twenty-four-hour period.

With the approach of pyrexia the urinary volume diminishes and the frequency of voiding may be decreased. In the two cases now under discussion the daily volume of the urine remained persistently below average throughout the period of observation (fig. 4).

Specific gravity. In keeping with the low volume of the renal output, the specific gravity of the urine is well above normal during the first five days in the case of Baby M. It is striking to note how renal concentrating power is called into action before the onset of pyrexia, how it increases pari-passu with the pyrexia, and how on the subsidence of the pyrexia it still follows a somewhat parallel course but is slower in its descent (fig. 1).

In the case of Baby B. it was not possible to demonstrate the increase in renal concentrating power by means of the specific gravity before the pyrexia, but the parallel though slower decline in the concentrating power of the kidney is well demonstrated (fig. 2). The wide difference between the specific gravity figures in these two cases and average figures obtained from apyrexial babies is well demonstrated in fig. 5 and in table 3. It implies that the kidney in the newborn infant is capable of concentrating the urine to a much greater extent than is usually recognized.

Urea. The concentration of urea in the urine is increased from day to day in the first five days in

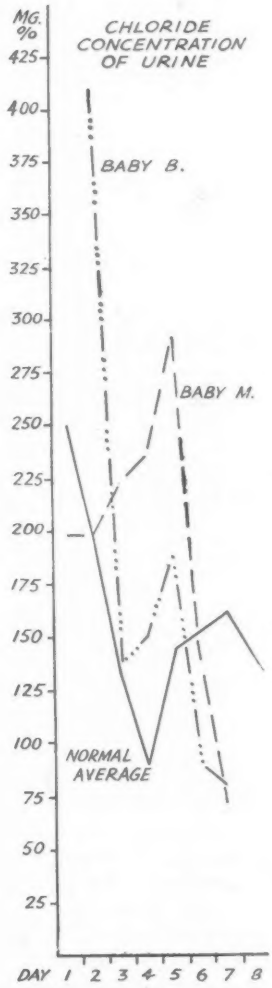

FIG. 7.—Chloride concentration of urine, babies M. and B. compared with normal average.

both cases. The increase is much greater and more rapid than is found in normal apyrexial babies (fig. 6). The figures recorded are greater than any of the figures which I recorded in apyrexial babies (Thomson, 1944). The urea concentration figures follow a somewhat parallel course to the specific

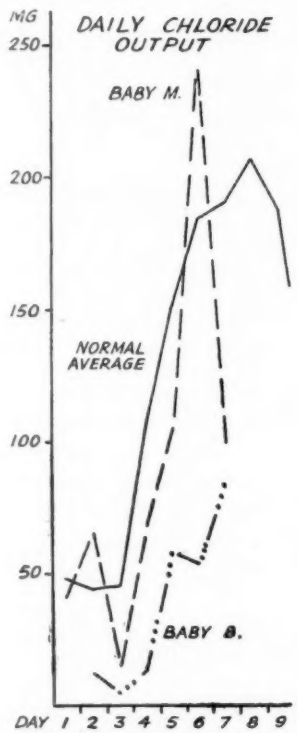

FIG. 8.—Daily chloride output, babies M. and B. compared with normal average.

gravity figures, the increase in concentration appearing before the onset of pyrexia and normal average figures not being reached till the eighth day.

Chlorides. In neither of the two cases now presented does the chloride concentration in the urine follow an average normal pattern (fig. 7). In the case of Baby M. the normal fall occurring in the first four days is replaced by an increase which subsequently falls below normal. It bears the same relationship to the pyrexia as is seen in the case of the specific gravity and concentration of urea (fig. 1). Despite the increased chloride concentration, at no time does the total daily output of chloride greatly exceed the normal (fig. 8). The curve of the chloride concentration in the case of Baby B., after falling from the initial high figure of 410 mg. per cent., approximates somewhat to that shown in the first instance. Excluding the initial high reading, the curve in this case, too, bears the same relationship to the pyrexia as does the specific gravity and urea concentration (fig. 2).

Summary

1. In two cases of dehydration fever in the newborn, the daily output of urine with its specific gravity, urea, and chloride concentration is recorded.

2. These observations are related to the time of onset and subsidence of the pyrexia.

3. The figures for the urinalysis are compared with those for normal average apyrexial newborn babies.

4. From the observations made it would appear that the kidney of the newborn infant is capable of concentrating the urine to a much greater extent than is generally recognized.

This investigation was carried out during the tenure of a Crichton Research Scholarship.

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THE ADDIS COUNT IN THE PROGNOSIS OF ACUTE NEPHRITIS IN CHILDHOOD*

BY

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The problem of assessing the extent of the renal damage following an attack of acute haemorrhagic nephritis has been the subject of much investigation. Renal function tests of various kinds have been described and undoubtedly are helpful if taken in conjunction with the clinical picture and the progress of the individual case. The reports of the prognosis of these cases, however, are still conflicting and therefore unsatisfactory.

Many of the tests depend on the rate of excretion of a chemical constituent of the blood or urine, e.g., urea, creatinine, water, etc., and, as might be expected, the results of various tests on the same patient are often remarkably uniform. Van Slyke's standard urea clearance test observes this principle and is deservedly popular, especially in adults where one can be reasonably certain of obtaining accurate samples of urine. In children, however, the collecting of specimens of urine is difficult, and it is probably true to say that the renal excretion tests in children are of less value than in adults.

In 1925, Addis introduced a method of assessing renal function by counting the cellular constituents of the urinary sediment. He evolved a standard technique and his results showed that he was able to detect abnormalities in renal function which were not apparent by the more usual excretion tests. In this way he was able to estimate the prognosis in cases of acute haemorrhagic nephritis (1931). The Addis count has also been found to be of value in assessing the renal damage in other diseases, e.g., erythema nodosum (Wallgren, 1939), rheumatic fever (Goldring and Wykroff, 1930; and Nathhorst, 1940), pneumonia (Goldring, 1931) and scarlet fever (Lyttle, 1933).

Addis (1925) standardized his technique as follows. Fluids were withheld during the afternoon and evening. At 8 p.m. urine was passed and discarded. Thereafter all urine passed until 8 a.m. was collected, that is, a twelve-hour specimen. The volume was measured. Ten ml. of the urine were then taken and, after centrifuging, reduced to a known volume, usually about 1 ml. which contained all the cellular elements of the 10 ml. of urine. Using a haemocytometer, the number of casts and cells (red cells and white cells along with epithelial cells) in the twelve-hour specimen of urine was estimated. The amount of protein in the urine was also measured by a modification of the method of Shevky and Stafford (1923) and the result given in milligrammes. The limits of normality in adults found by Addis are given in table 1.

Several articles have been published about the value of the Addis count in nephritis. Most of them confirm Addis' original findings (Van Slyke, 1930; Lyttle, 1933; Snoke, 1937; Cass, 1939; Murphy and Rastetter, 1938; Gachet, 1941; and Murphy and Peters, 1942). On the other hand Boyle and his co-workers (1937) stated that acute nephritis did not progress to a chronic stage. Only one Addis count, however, was done in each case and repeated counts might have been of more value. In 1942, Rubin and his co-workers, following forty patients with acute haemorrhagic nephritis during the acute stage, found that 120 days (seventeen weeks) were taken for the Addis red cell count to fall to the level of 1,000,000. This latter figure is taken by Soto (1942), as the upper normal limit. In view of the favourable comments on the value of the Addis count, it was decided to study the method in a series of cases at the Royal Hospital for Sick Children, Glasgow.

The Range of Addis Counts in Normal Children

In the first place, counts were made on the urine of a number of healthy children to establish normal values. The urines of twenty children who did not give a history of previous nephritis, rheumatism, or recent acute infection were examined and counts made. As already stated, the collecting of specimens of urine in children is often difficult and it was decided not to restrict the intake of fluid so rigidly as in adults. On the day of collecting the specimen of urine five ounces of fluid were given at 4 p.m. Thereafter fluids were withheld. The urine was then collected from 7 p.m. to 7 a.m. The count was made as described by Addis (1925). In any

* This work was carried out during the tenure of a Muirhead Scholarship.

TABLE 1

THE RANGE (R) AND THE AVERAGE (A) COUNTS OF CASTS, CELLS AND PROTEIN IN THE URINARY SEDIMENT OF NORMAL ADULTS AND CHILDREN AND THE PROPOSED UPPER NORMAL LIMITS IN CHILDREN

Series		Casts	Red cells	White and epithelial cells	Protein mg.
Addis (adults)	R–	0–4,270	0–425,000	32,000–1,835,000	—
	A–	1,040	65,750	322,000	30
Lyttle (children)	R–	0–12,916	0–129,000	9,000–2,822,000	3–47
	A–	1,085	15,181	322,484	18·5
Snoke (children)	R–	0–29,000	0–800,000	—	5–90
	A–	1,230	81,000	—	28·5
Author (children)	R–	0–6,350	0–438,000	9,000–714,000	3–45
	A–	1,175	61,325	329,500	22·5
Proposed upper limits		10,000	600,000	2,000,000	55

case where bedwetting was suspected, the urine was discarded. The results are given in table 1 along with those of Addis, Lyttle, and Snoke.

It will be seen that, although the ranges of results varied, the average counts in the present series are similar to those found in normal children and adults by other workers. It was noted that in many urines from these cases the cast count was zero and that the white cell count was often unduly high in female children who were not catheterized. Because of these facts, and from impressions gained during the investigation, it seemed that almost as much information was to be obtained from the red cell count alone as from all three counts. If this is so, it is of importance as it lessens the time necessary to carry out the count and thus increases its value as a clinical test. From the figures in table 1, it was accepted that a red cell count of over 600,000 in the twelve-hour specimen of urine was abnormal and should be regarded as an indication of renal impairment.

During the years 1938 to 1944, 236 cases of acute nephritis were admitted to the Royal Hospital for Sick Children, Glasgow. Of these children, 218 were examined and their renal function investigated. The whole course of the attack was followed throughout in forty-four of these; on re-examination of the other 174, the urine was tested for albumin and blood and the Addis counts were done on at least two occasions. In each of the latter cases more than one year elapsed between dismissal and re-examination. Indeed, twenty-nine were re-examined after one and a half to two years; thirty-six after two to three years; twenty-three after three to four years; twenty-three after four to five years; twenty-eight after five to six years; sixteen after six to seven years, and five at the end of seven years from dismissal. In addition, the blood pressure and the non-protein nitrogen (Folin and Svedberg, 1930) were estimated. If any of these tests were unsatisfactory, the serum proteins were estimated by the micro-Kjeldhal method, and the urea concentration test of MacLean together with the urea clearance test of Van Slyke was done.

On the findings of the Addis counts, the cases were classified as shown in table 2, and it was possible to compare the value of the Addis count with that of the other tests of renal function. It

TABLE 2

STAGE OF NEPHRITIS AT THE FINAL EXAMINATION (218 CASES)

Stage at present	Number of cases	Percentage of total
Recovered	159	72·9
Latent	41	18·8
Active	0	0
Terminal	3	1·4
Died	15	6·9
Total	218	

was found that 159 (72·9 per cent.) of the 218 cases had recovered, that is, all the tests including the Addis counts were normal. Forty-one cases (18·8 per cent.) were regarded as being in a latent stage. In sixteen of these there was mild albuminuria, and in all but one, in which the urine contained a trace of albumin, the Addis count (red cell) was raised. The other excretion tests were satisfactory in every instance. It will therefore be seen that in

twenty-five (41 – 16) cases the raised red-cell Addis count was the only indication that the renal function might still be active. This test, therefore, detects the presence of renal damage even when the blood pressure and the non-protein nitrogen are normal and the renal function found to be unimpaired by the urea clearance and concentration tests. When the latent stage is persistent, it is considered improbable that the renal lesion will heal. Snoke (1937) believes that if the Addis count does not return to normal within two years recovery is unlikely. The findings in the present series, where thirty-five of the forty-one cases have been in the latent stage for more than two years, would seem to confirm this belief.

In three cases (1·4 per cent.), all the tests were unsatisfactory and the Addis counts raised. As these children had had nephritis for over three years it may be assumed that the lesion was progressive and recovery unlikely. It was found, therefore, that the Addis count, although raised in the terminal stage of nephritis, was not more helpful than the more commonly employed tests. The appearance of the patient, the albuminuria, nitrogen retention, and poor urea concentration and clearance tests showed only too well the presence of marked and progressive renal impairment.

Of the fifteen patients (6·9 per cent.) who died, the cause of death was acute infection (nine cases), acute hypertensive encephalopathy (two cases), and uraemia (four cases). Two of the latter four cases died within twelve weeks of the onset of the initial attack. The other two progressed slowly over a period of years to a chronic stage with hypertension and nitrogen retention before dying in uraemia. The range and average Addis counts in each stage are given in table 3.

Of the 218 cases, forty-four, admitted between May, 1943, and December, 1944, were under observation from the onset of the disease. Addis counts were done at regular intervals. On dismissal, tests of the urine were normal in thirty-eight cases; in the other six there was a trace of albumin and an occasional red cell in the urine on microscopic examination. The Addis red cell count, however, in every instance was over 1,000,000 and in one instance as high as 20,000,000. The blood pressure, non-protein nitrogen, serum proteins, and urea concentration and clearance tests were satisfactory. It is, therefore, evident that on dismissal the Addis count in thirty-eight of these patients revealed evidence of renal mischief undetected by other tests.

The Addis counts were repeated at regular intervals after dismissal; in thirty-nine cases they returned to normal, but in five cases the red cell count has remained raised, indicating that the renal lesion is still present although possibly latent. It was found that in the thirty-nine cases the shortest time taken for the Addis count to fall below the upper limit of 600,000 was twelve weeks, the longest time fifty-two weeks, and the average time sixteen weeks. This average time is rather less than that given by Rubin and his co-workers (1942) who, taking an upper normal limit of 1,000,000 (Soto, 1942), found that this level was reached after seventeen weeks.

It was seen that thirty-six of the forty-four patients were dismissed from hospital within eleven weeks of the onset of the disease. As the red cell Addis count takes, on the average, sixteen weeks to return to normal, most of these patients were dismissed while the Addis counts were raised. The cases were regarded as recovered, at least temporarily, only when the Addis count and all the other tests were normal. Prolonged hospitalization may have a beneficial effect on the prognosis of the disease.

Illustrative Cases

The counts in two representative cases, one healed and one in the latent stage, are given.

E. T. (male), aged seven years, was dismissed on Feb. 11, 1944, four weeks after the onset of the initial attack of acute nephritis. On dismissal, the urine was clear to routine tests (see table 4).

H. W. (male), aged ten years, was dismissed on Aug. 30, 1943, seven weeks after the onset of a second attack of acute nephritis. (The first attack had been in October, 1938, and had lasted nineteen weeks.) The urine contained a trace of albumin on dismissal, but there was no nitrogen retention nor hypertension and the renal excretion tests were good.

TABLE 3

ADDIS COUNTS: THE RANGE (R) AND AVERAGE (A) ADDIS COUNTS IN EACH STAGE

Stage	No.	Casts	Red cells	White and epithelial cells	Protein mg.
Recovered ..	159	R. 0–8,650 A. 842	0–552,000 75,445	0–7,695,000 486,325	3–36 19·79
Latent ..	41	R. 0–22,600 A. 6,725	517,000–6,324,000 1,386,000	0–2,360,000 654,510	36–90 72
Terminal ..	3	R. 0–58,000 A. 16,840	960,000–3,670,000 2,071,330	45,000–4,860,000 1,635,000	320–1,230 735

TABLE 4
SUMMARY OF TESTS IN CASE E. T.

Date	Casts	Red cells	White and epithelial cells
1944			
Feb. 11	35,000	3,075,000	4,640,000
Mar. 9	11,200	1,481,500	1,865,000
Apr. 8	4,200	925,000	768,000
May 6	0	498,000	326,000
Aug. 18	0	322,000	196,000
Dec. 27	0	48,600	126,000
1945			
Apr. 19	1,200	54,300	286,000
Nov. 14	0	0	48,000

Since then, except for an occasional haze of albumin, the urine has remained clear. There has been no evidence of renal failure (see table 5).

TABLE 5
SUMMARY OF TESTS IN CASE H. W.

Date	Casts	Red cells	White cells
1943			
Aug. 29	92,200	28,700,000	3,280,000
Sept. 30	24,500	16,710,000	2,465,000
Oct. 26	11,400	2,890,000	1,480,000
1944			
Aug. 5	0	968,000	562,000
Oct. 10	1,240	1,031,000	834,000
Nov. 7	4,650	1,968,000	426,000
Dec. 12	11,850	7,020,000	5,125,000
1945			
Mar. 20	0	1,369,000	236,000
June 27	0	1,710,000	526,000
Dec. 23	16,450	6,256,000	5,853,000

It was suggested by Snoke (1937) and Gachet (1941) that recovery should not be considered to be complete until the Addis count had been normal on numerous occasions for at least one year. In the present series, 153 of the 218 cases had had normal Addis counts for more than one year and six cases for more than eight months. There had been no evidence of relapse in these cases. It can therefore be said that when the Addis count returns to normal and remains so on several examinations, the renal lesion has healed and that a relapse is unlikely.

Summary and Conclusions

A description of the Addis count of the urinary sediment is given. The normal limits for casts, red cells, and white cells in the twelve-hour specimen of urine are defined. The red cell Addis count is thought to give as much information as the cast or white cell count in children. In the twelve-hour specimen a total excretion of 600,000 red cells is given as the upper limit of normal.

Using the routine renal function tests as well as the Addis count, 218 cases of acute haemorrhagic nephritis were examined; 174 were investigated after the acute attack had subsided, and forty-four were followed throughout the course of the illness.

Forty-one of the 218 cases were found to be in a latent stage, and in twenty-five of the forty-one the raised Addis count was the only sign of a persisting renal lesion.

In each of the forty-four cases, which were under observation from the onset of illness, the Addis count was raised on dismissal from hospital, and in thirty-eight was the only indication of renal damage at that time. The Addis count (red cell) returned to normal within an average of sixteen weeks in thirty-nine cases, but in five has remained above the 600,000 level.

It is suggested that the Addis red cell count gives a better indication of the prognosis in acute haemorrhagic nephritis than any other test of renal function and that it should be more frequently employed in assessing the prognosis in individual cases.

I wish to thank Dr. Stanley Graham for his help and advice in preparing this paper.

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CASE REPORTS

GASTRIC DILATATION, MEGACOLON, AND IDIOCY IN IDENTICAL TWINS

BY

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The chief interest in the cases to be described lies in the association of atonic dilatation of the stomach, megacolon (Hirschsprung's disease) and the coeliac syndrome with idiocy, and in its occurrence in identical twins.

Family and Social History

The parents were well educated, the father being a master at a well-known public school. There were no mental or physical abnormalities of significance, apart from a history of twinning among cousins of one of the parents.

The first child of the family was born with difficulty, labour being long and terminated by forceps, her subsequent development, both physical and mental being normal. The twin conception took place eight months after the birth of the first child. For four months the mother was able to carry out her household duties in a normal manner, but at the end of that time her abdomen enlarged markedly. She felt sickly and ill, with vague indigestion and abdominal discomfort, which necessitated long periods in bed. Labour commenced March 16, 1938, six to seven weeks before full term, and was characterized by one pain for each birth with thirteen minutes between them. An excess of liquor amnii was passed, followed by a single placenta with two umbilical cords attached. A third pregnancy terminated uneventfully two years later, a normal child resulting.

Early History

The birth weights of the twins were identical, being 5 lb. 12 oz. each. On the third day both of them developed asphyxia, and went blue several times, the younger baby causing considerable anxiety that lasted throughout the day. The condition never recurred. Neither child was able to take the breast, though they were fed on breast milk from the bottle up to the end of the sixth week, when they were put on Cow and Gate. They gained weight very slowly, and at the end of the fifth week the elder (A) weighed 6 lb. 9 oz. and the younger (B) 6 lb. 6 oz. From then onwards their weights increased more quickly, so that in the sixteenth week they weighed 10 lb. 2 oz. and 10 lb. respectively.

Their bowel history up to this time gave no cause for alarm, but at five months both of them contracted what was called by the visiting practitioner 'summer diarrhoea.' In the case of B, this was followed by constipation with considerable abdominal discomfort that lasted twenty-four hours. Thereafter both of them became liable to alternate diarrhoea and constipation, occasioned by such trivial changes in the diet as alternating from Robinson's patent groats to Robinson's patent barley.

Both children were delicate and liable to coldness of the extremities. During teething, which began at ten months, B was liable to a rise of temperature up to 101° F., and at fifteen months A developed bronchitis and laryngitis with high fever. At seventeen months B began to crawl, but her sister made no efforts to do so. The delay in development was attributed to prematurity at birth, so that the possibility of mental deficiency was not entertained until they were about eighteen months old. Treatment with thyroid extract was instituted at this time, but no benefit resulted apart from some improvement in the condition of the peripheral circulation.

At twenty-one months they were seen by Sir Leonard Parsons, who diagnosed mental deficiency which he attributed to primary amentia. He reported that he could find no other cause for their backwardness, and that at this time they presented no indications of chronic abdominal disease. In their third year, however, the parents noticed that their abdomens at times were distended.

At two years five months the anterior fontanelle was not quite closed in the case of the elder twin, and had only just closed in the case of the younger. It was noted at this time that they showed a lack of initiative and imitativeness, that they appeared indifferent to the objects around them, and that they were unable to recognize their mother. They made no attempt at walking, talking, or feeding themselves, and their habits with regard to urination and defaecation were undeveloped.

At two years nine months B began to show some interest in walking, and before her admission to the

TABLE 1

	A	B
General appearance	In poor health, though of good colour and fairly well nourished	In poor health, though of good colour; rather thin
Height	33 in.	34½ in.
Weight	21 lb.	21 lb.
Eyes	Blue	Blue
Tongue	White fur	Clean
Teeth	Healthy	Healthy
Throat	Tonsils enlarged	Tonsils enlarged
Thyroid	Not enlarged	Not enlarged
Skin	Scarring on buttocks and vulva	Healthy
Heart	Apex beat in 5th interspace and mid-clavicular line. No enlargement of area of cardiac dullness. Tic tac rhythm. No adventititious sounds. Poor tone	Apex beat in 5th interspace. No enlargement of heart. Tic tac rhythm. Rapid action. No adventitious sounds
Lungs and respiratory system	Fair respiratory range. Slightly impaired percussion note. Harsh breath sounds; no adventitious sounds. Slight cough, and nasal discharge	Good respiratory range. No impairment of percussion note. Harsh breath sounds
Abdomen	Poor musculature of abdominal wall. Liver, spleen, and kidneys not palpable. Distension very marked. Flatus +. Small umbilical hernia. Considerable evidence of constipation	Divergence of recti. Thin musculature of abdominal wall. Liver, spleen, and kidneys not palpable. Distension very marked. Flatus ++. Small umbilical hernia
Lymphatics	Small discrete glands palpable in both groins, left axilla, and left cervical region	Small discrete glands palpable in both groins, axillae, and cervical regions
Optic discs	Impossible to examine	Impossible to examine
Pupils	Equal, regular, and central. React normally to light	Equal, regular, and central. React normally to light
Motor functions	Sits up and stands with support. Is unable to roll over on to her abdomen. Is unable to pick up a cube from the table or to hold two cubes. Shows no preference for right or left hand. Does not creep when laid prone. Is unable to walk, but makes stepping movements. Rocks from side to side continuously when in bed. Some purposeless movements of hands. Myoclonus present	Sits up and stands with support. Can roll over on to her abdomen. Is unable to pick up a cube from the table, or to hold two cubes. Shows no preference for right or left hand. Creeps when laid prone. Walks with difficulty, is slightly spastic, and has poor balance. Lies in bed in the opisthotonos position and swings herself, balanced on head and feet. Myoclonus present
Reflexes	Abdominal reflexes: present but diminished. Knee jerks; present and equal. Plantars: flexor (R. and L.)	Abdominal reflexes: not elicited. Knee jerks: present and equal. Plantars: flexor (R. and L.)
Sphincters	Wet and dirty in habits	Wet and dirty in habits
Sensory and receptive functions	No evidence of gross dysfunction of sight, hearing, or crude sensation, but does not understand anything that is said to her	No evidence of gross dysfunction of sight, hearing, or crude sensation, but does not understand what is said to her
Urine	No abnormal constituents	No abnormal constituents
Wassermann reaction	Negative	Negative

Colony she could walk with very little help, though she still showed no interest in toys of any description. A, however, remained greatly retarded in this respect, and in general appears to have been rather more backward and lethargic than her sister. She could balance herself sitting up, but could not pull herself up to the sitting position and was liable to throw herself backwards. Her chief occupation was watching her hands, which she used aimlessly though she soon tired.

At three, both of them developed whooping cough.

Condition on Admission

They were admitted to Stoke Park Colony on June 11, 1941, at the age of three years and three months; their physical and mental states were as given in table 1.

Attempts at mental testing established the incapacity of the twins for any degree of purposive activity. They were both unable to talk, or do anything for themselves. A refused to lie down. She would wave her hands aimlessly in the air, took no notice of words addressed to her, and would fall asleep swaying her body. She was miserable and fretful, and when offered toys she pushed them all away and refused to take anything into her hand. Both were quite incapable of doing any of the Terman-Merrill or Merrill-Palmer tests. B played with bricks only by throwing them on to the floor. She was very restless, and usually wanted to move about touching things all the time. On some occasions she spent much time gazing at one hand, but at other times she took no interest in her surroundings, was blank, salivated excessively, and cried frequently. They were both diagnosed as idiots, and were incapable of guarding themselves against common physical dangers, or of being taught to do so; their mental ages were assessed as considerably less than two years.

Progress after Admission

The twins were very liable to sickness, at first after almost every feed. The vomitus was offensive and mixed with sputum. A vomited even after small quantities of food.

There was some alternation in the frequency of their motions, towards diarrhoea and constipation, with corresponding alternation in their consistency, between fluidity and more solid whitish putty-like stools, when they were very foetid, so that ' it was almost impossible to go near.'

Both continued to show marked abdominal distension, this being more marked in the case of B than of A, and in order to relieve it enemata and the passage of the flatus tube were necessary from time to time. Their progress was interrupted by respiratory infections and what were considered to be bouts of intestinal toxaemia with fever, restlessness, recurring distension, constipation, and fretfulness. Coccal infections of the skin, such as boils

TABLE 2

	A	B
Height	39 in.	39½ in.
Weight	29½ lb.	31½ lb.
Skin	Multiple scarring from coccal infections	Multiple scarring from coccal infections. Extensive bald patches on the scalp
Heart	Apex beat localized in 4th left intercostal space, just internal to the nipple line	Apex beat localized in 5th left intercostal space, just internal to the nipple line
Lungs	No abnormal signs except for tympanitic resonance as high as the 8th left intercostal space behind, presumably due to gastric dilatation	No abnormal signs
Abdomen	Abdominal circumference variable in extent, average about 25½ in. Umbilical eversion. Distended abdominal veins. Gross abdominal distension. Abdominal palpation followed by considerable expulsion of foul-smelling flatus	Abdominal circumference variable in extent, average about 23 in. Abdominal distension less marked than in A
Central nervous system	Facial movements normal except for occasional twitching of right side. Manneristic rocking of head from side to side. Hyporeflexia affecting arm and ankle jerks. Positive Hoffman's sign —left. Walks with help with feet everted and bilateral pes planus. Urinary and faecal incontinence	Hippus occasionally noticed. Assumes opisthotonos position lying in bed. Absent triceps jerks and abdominal reflexes. Positive Hoffman's sign right and left. Normal gait. Urinary and faecal incontinence less marked than in A

TABLE 3

		A	B
Blood counts	Red cells	5,010,000	4,700,000
	Haemoglobin	80%	85%
	Colour index	0·80%	0·91%
	White cells	10,300	8,400
	Polymorphs	32%	50%
	Lymphocytes	65%	42%
	Large mononuclears	3%	4%
	Eosinophils	—	4%
Sugar tolerance Dose : 50 g. Dextrose	Fasting	71 mg. %	79 mg. %
	½ hour	228 mg. %	238 mg. %
	1 hour	284 mg. %	292 mg. %
	1½ hours	316 mg. %	224 mg. %
	2 hours	198 mg. %	174 mg. %
Blood calcium		9·5 mg. %	10·8 mg. %
Faeces (48-hours' excretion)		A fatty clay-coloured stool (weight 83 g.) of uniform consistency cutting like a fairly firm slab of butter. Dry matter 38·5%. Microscopic examinations revealed excess of soap crystals and plaques. No starch granules detected. Few partially digested meat fibres and cellular residues. Stercobilin much decreased (about ¼ normal). No bilirubin. Total fat: 30·4% of dried faeces. (Soap 20·8%. Fatty acids 7·6%. Neutral fat 2%.) Culture: b. coli and b. faecalis alkaligenes. No tubercle bacilli.	A fatty clay-coloured stool (weight 71 g.) of uniform firm consistency. Dry matter 33·8%. Microscopic examination revealed excess soap crystals and plaques. No starch granules detected. Few partially digested meat fibres and cellular residues. Stercobilin much reduced (about ¼ normal). No bilirubin. Total fat: 30·6% of dried faeces. (Soap 23·8%. Fatty acids 4·6%. Neutral fat 2·2%.) Culture: b. coli. and b. faecalis alkaligenes. No tubercle bacilli.

made their appearance from time to time, and B in particular was very liable to pull out her own hair from the scalp.

Their weights showed considerable variation with a tendency to alternate increases and decreases. During their six years in the Colony, A has gained 8½ lb. and B 10½ lb., in contrast with the normal average increment during that period of 28 lb.

(For photographs see Plate Va and b).

The present condition of the twins is given in table 2, and the laboratory findings in table 3.

Radiological findings of A. Radiography was complicated by the fact that the patient was a resistive idiot, but it was quite apparent that there was a tremendous ballooning of the stomach which led to upward displacement of the heart shadow (Plate Vc). The bones showed definite evidence of osteoporosis, especially in the long bones.

She was reluctant to take the whole quantity of barium meal and took two and a half hours to take 12 oz. A film at the end of two hours showed a forward rotation of the stomach which subsequent radiographs confirmed (Plate Vd). As the child had to be radiographed in a recumbent posture it seemed probable that the x-ray appearances were distorted by the projection of the spinal column against the stomach, this giving the impression of two separate loculi (Plate Ve). In this film at the end of four hours the greatly distended outline of the stomach was apparent with a small quantity of barium in the left 'loculus,' and a larger quantity in the right 'loculus.' Barium is seen in the small intestine, in which there is no evidence of dilatation. A film (Plate Vf) taken at the end of five and a half hours, showed the left 'loculus' to be empty, with the right 'loculus' partly emptying through the pyloric outlet, which appears to be situated more internally and posteriorly than usual. The colon began to fill at the end of five hours, and at the end of twenty-four hours most of the barium was situated in the ascending and pelvic colons.

A barium enema showed marked redundancy of the descending colon as well as considerable ballooning. The x-ray appearances, therefore, may be summarized as follows: There is marked displacement of the heart shadow upwards, due to enormous dilatation of the stomach and ballooning of the colon. There is evidence of redundancy of the colon as well as of megacolon (Plate Vg).

Radiological findings of B. Radiographs of the chest showed some upward displacement of the heart but not to the extent of that in A. The same tendency to biloculation was noted, but the emptying time of the stomach was much less than in A's, and half an hour after the barium was given there was a considerable amount of it in the coils of the small intestine (Plate VIh). The same effect produced by gastric dilatation was found with the duodenal bulb pointing internally and backwards (Plate VIj).

At the end of four hours the stomach was almost empty and at the end of four and a half hours the ascending colon was beginning to fill and was evidently dilated. At the end of twenty-four hours the meal was almost solely confined to the pelvic colon and rectum.

A radiograph after enema of 30 oz. of barium mixture showed marked reduplication of colonic shadow to the right, which was dilated in the whole of its extent up to the splenic flexure (Plate VIk).

Mental progress. Their scores by the Gesell standards best illustrated the mental progress of the twins while in the Colony, and these are summarized in table 4.

Evidence of uniovularity. In support of the twins being identical we have the mother's statement, confirmed by the doctor in attendance, of a single placenta. As regards other characteristics, we may summarize them as follows:

APPEARANCE AND GENERAL FEATURES. There is no doubt, as indicated by their photographs, that their general similarities of physique have been considerably modified by the various vicissitudes of their physical condition. The older twin presents a more angular facial outline with slight facial tic, while the younger has more rounded features.

HAIR COLOUR, TEXTURE, AND FORM. Their hair colour was identical. Two distinct shades were apparent, corresponding on Fischer's Scale to F11 (dominant) and F8 (subordinate). A's hair was of slightly finer texture than B's, which was attributed to her poorer nutrition. The hair of both was curly.

EYE COLOUR AND IRIS PATTERN. Both had the same shade of bluish irides without any marked features of iris pattern.

SKIN COLOUR AND COMPLEXION. Both had fresh complexions and skin of fine texture, though again some differences were attributable to the different state of their nutrition.

EYELASHES, EYEBROWS, LIPS, SHAPE OF EARS, SHAPE, SIZE, AND ARRANGEMENT OF TEETH. Eyelashes and eyebrows were of an identical colour, form, and texture. The lips showed slight dissimilarities in that B's were rather thicker, and A's were slightly contorted by the facial tic, though their underlying structure was the same as B's. The shape of the ears was identical, though B's were slightly more fleshy. The shape and size of the teeth were identical but there were differences in arrangement which could have been due to variations in eruption consequent on faulty nutrition.

HANDS AND FINGERS. Shape and size showed close similarities. Attempts at procuring finger prints were not very successful and ridge counts were impossible to obtain. Finger nails and lunulae were identical.

MIRROR IMAGING. We could find no evidence of mirror imaging in regard to handedness, dental irregularities, and palm patterns, though evidence was found of mirror imaging in the pattern of the hair whorling as it curled in opposite directions on combing.

BLOOD GROUPS. Blood groups were identical as established by Dr. Tovey (Regional Transfusion Officer).

TABLE 5

	A	B
Blood Group	B	B
Rh type	Rh_1 Rh_2 (CDEc—positive)	Rh_1 Rh_2 (CDEc—positive)
M.N.	Type N	Type N

Commentary

The cases are of interest on account of the association of idiocy with gastro-intestinal abnormalities, both apparently genetically determined since they occurred in identical twins. The precise

TABLE 4

	A	B
Motor development :		
4 months' level	4½ successes out of 7 tests	5 successes out of 7 tests
6 months' level	1 success out of 5 tests	2 successes out of 5 tests
9 months' level	2 successes out of 5 tests	3 successes out of 5 tests
Language	No successes beyond 4 months' level	No successes beyond 4 months' level
Adaptive behaviour :		
4 months' level	2 successes out of 3 tests	2 successes out of 3 tests
6 months' level	No successes out of 6 tests	1 success out of 6 tests
9 months' level	No successes	No successes
Social behaviour :		
4 months' level	1 success out of 6 tests No successes beyond 4 months' level	2 successes out of 6 tests No successes beyond 4 months' level

nature of these abnormalities does not appear to coincide with any previously recorded. The nearest approach to cases similar to ours are those described by Joseph Popper (1920), who reported megacolon in twins, one of whom died on the fourth day of its life, the other being diagnosed at the end of four weeks. That there is some degree of megacolon in the present cases is shown by the radiographs, though it is not as extreme as has been found in other cases. On the other hand the patients were resistive when the barium enema was being injected, and probably, but for this, greater dilatation could have been demonstrated. The onset of the condition presumably followed an attack of acute gastro-enteritis at five months, which may indicate some dependence of genetic factors on environmental, i.e. infective. We think that this dependence is much closer than is usually recognized. The cases also have some similarity with that described by Moncrieff and Crichlow (1944) in which dolichocolon was diagnosed by radiograph at ten months and terminated fatally as Hirschsprung's disease at thirty months. The authors remark that their case throws considerable doubt on the usually accepted ideas as to the etiology of Hirschsprung's disease, and especially as to the applicability of the term 'congenital idiopathic dilatation of the colon.' A degree of dolichocolon is to be noted in our cases. Dissimilar features, however, are the occurrence of a partial coeliac syndrome along with considerable gastric dilatation. The coeliac syndrome is indicated by considerable retardation of growth (height 33 in. and 34½ in. respectively in June, 1941, 39 in. and 37½ in. respectively in June, 1947, in contrast to the norms 37 in. at 3¼ years and 51 in. at 9 years), frequent fatty stools, abdominal distension in contrast to the general emaciation of the body, and gluteal wasting. The radiological findings in idiopathic steatorrhoea were discussed by Brailsford (1943), who comments on changes in the small intestine and the bones. He reported evidence of irregular tonicity, and a more rapid flow through the intestine so that after two hours barium was seen throughout the whole course of the large intestine. Dilatation of jejunum and large intestine were also noted. Snell and Camp (1934) commented on the smooth contour of the proximal part of the jejunum, which appeared hypertrophied, with clumping of barium in smooth elongated masses. Atrophy and dilatation of the whole tract were also noteworthy features, though no specific reference was made to gastric dilatation.

Six out of eight cases examined radiologically by Bennett et al. (1932) after the administration of barium enemata showed abnormal dilatation of the colon, from moderate degrees affecting the descending colon only, to an extreme dilatation involving the whole of the large bowel and sufficient to justify the term 'megacolon.' Gastric dilatation, however, does not so far appear to have been described in this connexion.

The occurrence of coeliac disease in identical twins has been noted on four previous occasions during the last fifteen years (Fanconi, 1928; Cervini et al., 1940; Collishaw, 1940; and Holmgren, 1945).

Our sincere thanks are due to Dr. R. M. Norman, Medical Superintendent, Stoke Park Colony, for his kind permission to publish the account of these cases. It is a pleasure to acknowledge his encouragement, helpful criticism, and active interest. Sir Leonard Parsons willingly consented to give us access to his case notes, for which we are deeply indebted. We are grateful to Dr. Tovey of the South-west Regional Transfusion Centre for his expert knowledge and for establishing the identity of the blood groups, and to Mr. A. H. Tingey, M.A., Clinical Pathologist, Stoke Park Colony, for his assistance with the laboratory investigations. We are indebted also to Mr. H. Cox, the radiographer, and to the nursing staff at Stoke Park Colony for their willing co-operation. Mr. T. J. Shields of the British Medical Association Library has perused the previous reports of similar cases, and to him our sincere acknowledgments are also due.

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(For illustrations to this article see Plates V and VI, pp. 257-8.)

PURPURA AND INTUSSUSCEPTION

BY

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As early as 1808 Willan described visceral crises occurring with purpura. Henoch published his classical paper in 1874, after which date abdominal purpura became associated with his name. The first report of intussusception with purpura appears to have been that of Vierhuff (1893). Since then, as far as can be ascertained, this combination has been reported only nineteen times. It is for this reason and because of the many interesting points this condition raises that a further case is recorded.

Case Report

A male child aged four years and eight months was admitted to hospital on Nov. 12, 1946. A month earlier he had had an attack of abdominal pain and vomiting which subsided rapidly and which was labelled 'chill on the liver.' Otherwise his earlier childhood had been uneventful except for measles, whooping cough, and tonsillitis. He was an only child. Both his parents were healthy and had not suffered from any of the allergic diseases.

Four days before admission he complained of pain in his left knee and the mother noticed that there was much swelling. The next day his right elbow became swollen and painful. He was then taken to his doctor, who diagnosed rheumatic fever and prescribed sodium salicylate. On Nov. 12 the swelling of his left knee had subsided but his right elbow and right wrist were painful. At noon on this day he suddenly developed severe abdominal pain, which was soon followed by vomiting. At the same time purpuric spots were observed on buttocks and right arm and he was transferred to hospital as a possible case of Henoch's purpura. His bowels had been regular until then, and no blood was noticed in the stool passed that morning.

On examination he was found to be normally developed and thin. He was apyrexial and quite alert. His skin was of striking pallor, but the conjunctival mucosa was well coloured.

Joints. He complained of no pain in the joints, and all movements were unrestricted and painless. There was some swelling of his right elbow, and possibly also of the right wrist.

Rash. A crop of petechial haemorrhages was found on his buttocks which, according to the mother, had been larger and more distinct a few hours previously. On the outer side of the swollen right elbow he had an extensive ecchymosis, and in the right cubital fossa there was one definite purpuric spot. He also had a boil on his right thigh. No urticarial lesions were seen.

Abdomen. Liver and spleen were not palpable. In the right iliac fossa a hard irregular mass was felt which was very slightly tender. It could be readily moved up and down but less easily sideways. It appeared to be in the peritoneal cavity. It occupied most of the right iliac fossa. A knob on its outer side was attached to the main mass. On rectal examination semi-solid yellow faeces without blood were found, and no other abnormality was detected. Cardiomuscular, respiratory, lymphatic, and central nervous systems appeared normal.

INVESTIGATIONS. The Mantoux test, 1-10,000, was negative. Red blood cells numbered 6,180,000 per c.mm. of blood; haemoglobin was 120 per cent., colour index 0·9, white cells 18,100 per c.mm., polymorphs 76 per cent., lymphocytes 20 per cent., monocytes 4 per cent., and blood platelets 238,000 per c.mm.

There was a trace of albumin in the urine; no red blood cells were seen. Culture was sterile, and there was a yellow reduction of Benedict's solution.

Bleeding time was 2½ minutes, coagulation time 3¾ minutes, and the tourniquet test negative.

A tentative diagnosis of purpura with rheumatic (Schönlein's) and abdominal (Henoch's) symptoms was made, but in view of the abdominal mass the possibility of intussusception could not be excluded.

PROGRESS. On Nov. 13 he vomited watery fluid once during the night. He had no appetite and became more dehydrated. The abdominal lump could still be felt. Intravenous therapy (glucose saline and plasma) was begun. Next day he was still vomiting and the petechiae were paler. At the advice of the paediatric consultant, expectant treatment was continued.

On Nov. 15 his general condition had deteriorated, anorexia, vomiting, and dehydration being marked. There had been no bowel action since admission. The cardiac rate was now 150 per minute, although temperature was still normal. The vomit contained upper intestinal contents. The abdomen was more distended; and the lump, unchanged in size and shape, was slightly more tender. Purpura was still

present but only very faintly. In spite of dehydration there was now frequency of micturition and the urine gave an orange reaction to Benedict's solution and contained ketone bodies. Capillary blood sugar at 4 p.m. was 313 mg. per cent. The occurrence of diabetic symptoms was considered to be due to a temporary toxic exhaustion of islet function.

As conservative measures, continued over three days, had not resulted in any improvement, as the abdominal mass had remained unchanged during the time of observation, and as the child had become extremely ill from acute intestinal obstruction, laparotomy was decided on. The intravenous drip was carried on throughout the operation and during the next two days. Penicillin (15,000 units every three hours) was given intramuscularly, and soluble insulin in doses of twenty units at 4 p.m., at 5.30 p.m., and again at 7 a.m. the next day, when his urine still gave a green reaction to Benedict's solution.

OPERATION. At operation (under nitrous oxide and ether anaesthesia) blood-stained fluid appeared when the peritoneum was opened. An irreducible ileo-ileal intussusception was found, with its apex about six inches from the ileo-caecal valves. This was resected from four inches above to two inches below the intussusception and a side-to-side anastomosis performed to restore the continuity of the gut. Rapid examination of the peritoneal contents showed no purpuric haemorrhages. The wound was closed in layers. The removed specimen consisted of about eight inches of intussuscepted small intestine causing haemorrhagic infarction.

On Nov. 16 the general condition was much better. The pulse was full and good, and there was no further vomiting. At 3.30 p.m. the child became suddenly worse and failed to respond to questions. He was unable to swallow and had a squint and a right plantar extensor response. As this attack occurred so rapidly, and more than eight hours after his last dose of soluble insulin, it was not considered to be due to hypoglycaemia, particularly as his intravenous glucose saline infusion was still in progress. The blood sugar was, however, not examined. The possibility of a purpuric intracerebral haemorrhage was dismissed as unlikely. The attack was probably due to a small cerebral embolus. On the next day he was gradually regaining consciousness, and by Nov. 18 was fully conscious, talking, and swallowing well, with no abnormal neurological signs. At this and subsequent examinations there were no reducing substances in the urine. The temperature was 100° F., and there was pneumonic consolidation in the right upper lobe. Sulphadiazine was begun in addition to penicillin, and the intravenous drip discontinued.

On Nov. 20 the chest was beginning to clear, the abdomen was soft, and the temperature 99° F. There was pain and swelling in both wrists and the left elbow, but no rash. Sodium salicylate, gr. 15 four-hourly, was begun. By Nov. 23 the pains and swelling in the joints had subsided, but there were petechial spots on both elbows. He vomited after taking salicylate, so this was changed to aspirin tablets and to calcium aspirin gr. 10, three times a day. Sulphadiazine was discontinued.

On Nov. 24 the rash round the elbows had become more profuse. Some spots were truly petechial, others were raised. At night the temperature was still 99° F. By Nov. 25 there was swelling and bruising of the right metacarpo-phalangeal joint of the right thumb, with recurrence of swelling of right wrist and dorsum of the right hand. There was more purpura also on the left elbow, but no other petechiae were seen. The chest was now clinically clear, and penicillin and all salicylates were stopped. He was afebrile.

On Nov. 29 he complained of abdominal pain and pain in the right lower chest. There were no abnormal signs. On Dec. 11 a swelling appeared over left tempero-mandibular joint, and also over the right frontal region and in the right knee joint. The temperature had risen to 102° F. by next morning, but gradually fell to normal by Dec. 17. The right testis was tender and slightly enlarged. A radiograph of the skull showed nothing abnormal.

By Dec. 17 he was afebrile and symptom-free, the bowels were regular, the abdomen soft, and there were no signs or symptoms in the joints and no urticarial or purpuric eruptions. The blood sedimentation rate was 40 mm. in the first hour.

On Dec. 31 he was transferred to Queen Mary's Hospital, Carshalton. Radiography of chest, joints, and long bones revealed nothing abnormal. The blood sedimentation rate varied between 35 mm. and 10 mm. per hour up till the middle of March, 1947, and has been normal since then. He has had several short febrile episodes, one accompanied by abdominal pain, two by finger sepsis, and one by neck pain radiating in turn to either ear. He has received dental treatment and has had aspirin administered for several weeks. No further purpura has been noted.

In July, 1947, there was a further attack of abdominal pain, accompanied on one occasion by passage of bright red blood. There were no other purpuric manifestations, and he was symptom-free after two days.

Analysis of this and Previously Reported Cases

Sex. Of the twenty cases under review, sixteen occurred in boys. The large preponderance of boys is significant and exaggerates a similar sex irregularity found amongst patients with so-called Henoch's purpura without added complications. McKechnie (1911) in fact states that all his cases of Henoch's purpura at Vancouver occurred in boys, although other observers have described this condition also in girls. Non-purpuric intussusception also is said to be two to three times more common in males than in females (Mitchell-Nelson, 1946). The male incidence of 80 per cent. in the present series may therefore be explained by either condition alone or

by the combination of intussusception and purpura.

Age. The average age of the twenty cases is 9½ years. Excluding the four adults of 21, 31, 29, and 21, the average age of the remaining sixteen children becomes nearly six years, which is a figure very much higher than that of intussusception without purpura. Indeed not one patient was under three years old, whereas the non-purpuric intussusception occurs most commonly in young children under three. On the other hand the age distribution tallied well with that of anaphylactoid purpura generally. This fact is important and supports the supposition that purpura is the primary condition.

Symptomatology. The initial symptoms and signs described in these cases differ in no way from those of non-thrombocytopenic purpura with abdominal symptoms. Their duration before intestinal obstruction becomes manifest is very variable. Most of the children were ' not well ' for a few days to a few weeks before the onset of intestinal blockage. Döbeli's (1908) patient gave the longest history. For about five years he had had abdominal and joint pains which were considered to be due to lead poisoning or rheumatism. Gara's (1912) patient suffered from ' purpura simplex ' for two years before intestinal symptoms developed. At the other extreme is Gamstedt's (1933) patient, in whom only three days after the onset of symptoms an irreducible intussusception was found at laparotomy.

JOINT PAINS. In eleven out of seventeen patients joint pains and swellings were described, eighteen months to two days before the obstruction. A not unusual story is that the joint symptoms subsided rapidly with or without salicylates and that the intussusception occurred shortly afterwards. This happened in the present case and in the one reported by Robinson (1910) and Döbeli (1908).

PURPURA. Purpura in some form or other was invariably present, and indeed its presence forms part of the diagnosis. Sutherland (1909) regarded a case of Still's (1909) where no haemorrhagic manifestations were described as one of anaphylactoid purpura. Nowadays, however, we would classify this particular patient as having suffered from chronic recurrent intussusception. In this series in practically every patient some cutaneous manifestations were obvious: at times a few isolated pin-point petechiae around the elbow joints or over the buttocks, at times larger ecchymoses, were seen. Haematuria is mentioned in four of the cases. Nose bleeds and vomiting of blood were recorded only once. An interesting symptom, which is not usually referred to in this connexion, is pain, swelling, and sometimes discoloration of the scrotum, which are described by Lett (1908b), Lederer (1913), Tonking (1910), and in my patient.

INTUSSUSCEPTION. Of particular clinical interest and of vital importance is the diagnosis of intussusception in this condition. Sutherland. referring to intussusception and abdominal purpura, stated in 1909, ' We do not seem to possess any reliable means of distinguishing these two affections, and even now, nearly forty years later, the problem is still equally difficult. Far more patients with purpura and abdominal symptoms are suspected of intussusception and are operated on than are actually found to have this condition. Very many cases of this kind have been reported in the literature, and many more have undoubtedly occurred, for example, Bailey (1930), Burrows (1904), Sutherland (1904), FitzWilliams (1908). The most tragic of these is probably that of Sutherland's; he, having advised laparotomy on one of his patients, who turned out to have no intussusception, refrained from operating on a very similar case shortly afterwards, and the child died from peritonitis due to intestinal invagination. A similar disaster was fortunately, but only barely, avoided in my own case.

There is not one symptom which clearly differentiates the two conditions. Bailey (1930), discusses the differential diagnosis between non-purpuric intussusception and Henoch's purpura, and Althausen et al. (1937), try to clarify the matter by tabulating the essential symptoms and signs. The younger age, abdominal tenderness disappearing between colics, absence of bleeding (haematemesis, petechiae, haematuria, and joint symptoms), and particularly the presence of a sausage shaped mass are all in favour of intussusception. None of these pointers are of course relevant to our present problem, where both phenomena are present at the same time. An abdominal mass has been felt frequently in uncomplicated purpura, and may have been due to bleeding into the intestinal wall (Greig, 1908), or lumen (FitzWilliams, 1908), to haemorrhage into the mesentery (Lett, 1908a), or omentum, to localized oedema and extravasation of fluid into these organs, to faecal masses, or even to the imagination of the observer. On the other hand, in the present series were at least six cases where no tumour was felt but the intussusception was discovered by operation (Hall, 1908; Collinson, 1910; de Lavergne, 1927), autopsy (Sutherland, 1909; Gara, 1912) or when passed per rectum (Lederer, 1913). Even vomiting was absent three times (Lett, 1908; Döbeli, 1908; Robinson, 1910). The presence or absence of blood in the stools also is of little significance. Reviewing all the cases, one can only say that a sudden worsening of the condition of a purpuric patient, if accompanied by severe colicky abdominal pain and vomiting, by absolute constipation (or the passage of bright red blood without faecal material or flatus), and by the appearance of an abdominal lump which changes little on repeated examination, should provide a strong indication for laparotomy. If this dictum is followed many children will be unnecessarily submitted to laparotomy, as has hitherto occurred. But the risk of an unnecessary operation must be very much smaller than that of leaving an intussusception untouched (Schwartzman, 1940).

All the patients in the present series have had

TABLE OF REPORTED CASES OF PURPURA WITH INTUSSUSCEPTION

No.	Author	Sex and Age	Joint Symptoms	Purpura	Vomiting	Blood p.r.	Haematuria	Mass	Site of Intussusception	Treatment	Result and Remarks
1	Vierhuff (1893)	M. 29				+			Ileo-caecal.	No operation.	Intussuscepted piece of bowel passed per rectum. Recovery.
2	Lett (1906)	M. 3	+	+	0	+	0	R. Loin.	Ileo-caecal. Ileo-ileal	Reduced. No operation.	Recurrence of intussusception three days after reduction of first. Died.
3	Hall (1908)	M. 5½	+	+	+	0	0	0	Ileo-ileal.	Resection.	Died.
4	Döbeli (1908)	M. 8	+	+	0	+	+	Left hypochrondrium at intervals.	? Sigmoid colon.	Enemas of glycerine and oil.	Recovered. Frequent relapses of intestinal obstruction, purpura, and intestinal masses. Presence of intussusception not proved.
5	Sutherland (1909)	F. 7	0	+	+ with blood.	+	+	0	Ileo-caecal.	No operation.	Died. General peritonitis at necropsy.
6	Morse and Stone (1909)	F. 7	+	+	+	+	0	R.I.F.	Ileo-colic.	Reduction.	Recovery. Recurrence of vomiting, purpura, intestinal bleeding. At laparotomy, nothing abnormal.
7	Collinson (1910)	M. 4	+	+	+	0	0	0	Ileo-ileal.	Insertion of Paul's tubes.	Resection 3 days after preliminary operation. Recovery.
8	Tonking (1910)	M. 5½	+	+	+	0		Above umbilicus.	Ileo-ileal.	Reduction.	Recovery.
9	Robinson (1910)	M. 5	+	+	0	+		Below umbilicus.	Ileo-ileal.	Reduction and resection.	Affected bowel also resected because of mesenteric thrombosis and gangrene. Recovery.
10	McKechnie (1911)	M. 10	0	+	+	+	+	Right of umbilicus.	Ileo-ileal.	Reduction.	Died several months later from nephritis.
11	Gara (1912)	M. 5	0	+	+	+ after enema.	+	Right of umbilicus. Not felt afterwards.	Ileo-caecal.	No operation.	Died.
12	Lederer (1913)	M. 12	+	+	+	+	0	0	?	Necrotic piece of intussuscepted intestine passed 5½ weeks after onset of symptoms. Recovered.	
13	Barling (1913)	M. 4	0	+	+	+		Epigastric.	Ileo-colic.	Resection.	Recovered.
14	de Lavergne and Guillemin (1927)	M. 21	0	+	+	+	0	0	Ileo-ileal.	Resection.	Died.
15	Caizergues (1929)	F. 3							Ileo-ileal.	Reduction.	Recovered.
16	Ballin and Morse (1930)	M. 31	+	+	+	+		Right of umbilicus.	Ileo-caecal.	Reduction.	Death 3½ months later from haematuria, nephritis, purpura. At autopsy many sub-peritoneal haemorrhages leading to ulceration, perforation, and peritonitis.
17	Gamstedt (1933)	F. 7	0	+	+	0	0		Ileo-ileal.	Resection.	Recovery.
18	Gray (1936)	M. 21	+	+	+	+		+	Ileo-caecal.	Reduction.	Recovery. Six days after reduction once more developed signs of intestinal obstruction. At operation kinking of terminal ileum over gangrenous patch in caecum. Lateral anastomosis performed.
19	Schwartzman (1940)	M. 3	0	+	+	+	0	Indefinite.	Ileo-caecal.	Resection.	Died day after operation. Family history of allergy.
20	Wolfsohn (1947)	M. 4	+	+	+	0	0	R.I.F.	Ileo-ileal.	Resection.	Recovery.

some purpuric symptoms for a few days before the onset of intestinal obstruction. If, with the above indication, laparotomy is undertaken but no intussusception is discovered, the most likely findings will be purely those of so-called Henoch's purpura. According to Holubec (1935), this may be complicated by duodenal perforation or appendicitis, and either of these may therefore have given rise to the serious symptoms. Alternatives, particularly in the slightly older age group may be what Sheppard Siegal (1945) describes as benign paroxysmal peritonitis, where a reversible inflammatory reaction occurs in the peritoneum, joint-lining, and other endothelial membranes. Some of Siegal's patients came to laparotomy. Further differential diagnoses to be considered are severe constipation, appendicitis (Holubec, 1935; Whitmore and Peterson, 1946), intestinal obstruction of other types, and acute regional ileitis (Mailer, 1938). Barnes and Duncan (1941) actually made the latter diagnosis at laparotomy, but when the abdomen was reopened ten days later no abnormality was detected and purpuric manifestations made them alter the diagnosis to one of anaphylactoid purpura.

Treatment and Outcome (see table)

Of the twenty cases under review, fifteen came to operation. Of the remainder, in two (cases 1 and 12) the piece of intussuscepted intestine sloughed away and was passed per rectum. In two (cases 5 and 11) the diagnosis was only made at necropsy, and in one (case 4) we have no absolute proof that a true invagination actually occurred. Lett's patient (case 2) had a further intussusception three days after the reduction of the first. This had to be left owing to the child's condition, and he died. Gray's patient (case 18) developed signs of obstruction six days after the reduction, and this was due to kinking of the terminal ileum over a patch of gangrenous caecum. The patient recovered after a lateral anastomosis had overcome the blockage. Case 6 had to be reopened a week after the reduction of an ileo-colic intussusception because of a recurrence of abdominal pain, vomiting, and bleeding, but no abnormality whatever was found at this second operation. Immediate resection had to be performed on seven occasions, with four resulting recoveries. In one of these (case 9) the invaginated bowel could be reduced but had to be excised owing to the presence of mesenteric thrombosis and resulting gangrene. One child had the affected loop resected three days after an initial ileotomy and he recovered (case 7). Two patients (cases 10 and 16) died several months after successful operation, one from nephritis, the other, who also had nephritis, from peritonitis due to the perforation of haemorrhagic intestinal ulcers. Altogether twelve of the twenty patients recovered and, as far as is recorded, no further recurrence of either intussusception or even purpuric symptoms occurred later than a year after the abdominal catastrophe.

Discussion

The nature of anaphylactoid purpura has been frequently discussed and the present case will throw no further light on the subject. In common with most reported cases, our patient presented no family or past history of allergic disease. No precipitating factor could be elicited to account for his illness, and no eosinophilia was encountered. At first it was thought that purpura may have been the response to the administration of salicylates, but when aspirin and salicylates were given on a third occasion during his convalescence no adverse reaction occurred. At any rate salicylates do not usually lead to this kind of purpura in susceptible subjects.

Several theories have been advanced to explain why intussusception should occur in these patients. The first assumption is that purpura and intussusception occur independently, and that each happens without being influenced by the other. Against this view must be held the rarity of each of the two conditions, so that the chances of a simultaneous occurrence of both must be infinitesimally small. Furthermore, the age incidence of intussusception in the present series is significantly higher than is found with non-purpuric cases. This argument can be used also against the second possibility, that intussusception is the primary condition and that purpura follows as a secondary, presumably toxic, complication. Döbeli (1908) believed that a gastro-intestinal disorder, such as peptic ulceration, intussusception, or enteritis, could be found in most cases if looked for, and that through absorption of bacteria or toxins abdominal purpura resulted. He stated that only by dealing with the underlying disorder could purpura be cured. All the data, however, speak against this idea. In practically every one of the twenty cases in this series there was a clear onset of intestinal obstruction, and this was invariably preceded (and not followed) by evidence of purpura. In my own patient rheumatic symptoms and petechiae occurred three and one days before severe abdominal pain and vomiting developed. During convalescence this boy had several bouts of purpura but intussusception apparently did not recur. Even in the case described by Döbeli himself, haemorrhagic manifestations appeared some time before the onset of abdominal pain and masses, and his diagnosis of chronic recurrent intussusception of the sigmoid flexure was never proved. His may well have been a case of purely abdominal purpura. Moreover, Döbeli's theory fails to explain the great frequency of the intestinal diseases he mentions without the co-existence of purpura.

This leaves the third and most likely possibility that intussusception develops as a complication of purpura. It has been assumed that a blood clot in the bowel lumen may act mechanically by its weight and thus cause this portion to be invaginated. This seems an inadequate explanation. Hall (1908), thought that the straining from vomiting during the

gastro-intestinal crisis of Henoch's purpura could lead to intussusception, and Althausen et al. (1937) consider amongst numerous causes of intussusception the presence of spasm in the intestinal segment above a partial hold-up, this spasm corresponding to the colicky pains experienced by the patient. Most observers agree that either extravasation of serous fluid, or especially haemorrhage into the mucous, submucous, muscular or subperitoneal coats of an intestinal segment are the main precipitating factors to produce the invagination. Intense congestion would invariably ensue. The actual intussusception could thus be the result of thickening of the bowel wall from haemorrhage, oedema, and congestion, this leading to partial obstruction, and a secondary paralysis of the affected intestinal segment with spasm and over-action of the portion above it. This theory appears to fit most of the known facts and agrees with many of the operative findings.

Summary

A case of purpura with intussusception followed by resection and recovery is described, and the literature of similar cases is reviewed. The symptomatology, etiology, diagnosis, and treatment of this condition are discussed.

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TUMOUR OF THE OPTIC CHIASMA

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Tumours arising in the small area at the base of the brain between the optic chiasma and cerebral peduncles are common and include meningiomas, suprasellar and pituitary neoplasms, aneurysm of the circle of Willis, and chiasmal arachnoiditis with cyst formation. Tumours arising in the optic chiasma and nerve sheaths, however, are very uncommon. In all these conditions, visual symptoms may obtrude to a degree that renders clinical differentiation difficult. In the case of chiasmal glioma here reviewed, diagnosis was much simplified by the characteristic radiological features.

Case Report

A bright and alert male child aged five and a half years was referred because of defective vision in the right eye. There was nothing relevant in the past history. He was the elder of two children of normal parents. Pregnancy and labour were normal and the birth weight was 6 lb. 5 oz. He had been artificially fed from birth, he thrived and developed well, and all the milestones were normal. At the age of fifteen months he had a sore throat with an accompanying convulsive episode attributed to high fever. Three months later he contracted measles and again exhibited two tonic convulsions in association with a high temperature. Unconsciousness lasted two minutes on each occasion. These febrile convulsions are in keeping with the cortical dysrhythmia which was found later in the electroencephalogram, and which was presumably of the inherited type as both his father and younger sister had convulsions under similar circumstances. He had remained perfectly well until two and a half months before admission, when he complained of a slight headache, frontal in distribution, worse in the evening and improving in the morning. He had two further headaches of similar nature. The parents consulted an ophthalmologist, who reported that the child was blind in the right eye, the left being normal. The child never complained that he could not see, nor had his school mistress suspected defective vision. There was no nausea, vomiting, polyuria, polydipsia, or loss of weight.

On examination it was found that the child's faculties were normal. He was not ill, nor in any discomfiture. There was no jaundice, cyanosis, dyspnoea, or oedema. Temperature, pulse rate, and respiration, heart, lungs, and abdomen were all normal. Blood pressure was 100/60 mm. Hg. There was no external evidence of neurofibromatosis. The child appeared normally proportioned—weight 37 lb., height 42 in., span 42 in., symphysis to vertex 22 in., symphysis to ground 20 in., skull circumference 20·5 in. No neck rigidity or murmurs on auscultation of the skull, and no exophthalmos or ptosis were noted. All the cranial nerves except the second appeared normal. Central vision in the right eye was absent, but on confrontation tests movements were perceived in the temporal field. Consensual and light reflexes were present, but the contraction of the right pupil to light was not as full as the left nor as well maintained. The optic disc was white, its edges sharply defined and the vessels normal. Vision in the left eye was full, but the disc was paler than normal, especially of the nasal half. Accurate plotting of the visual fields was impossible because of the child's age. The eye findings were interpreted as a large central scotoma of the right eye with well marked optic atrophy and commencing atrophy of the left disc. The rest of the cranial nerves and central nervous system were normal.

LABORATORY STUDIES. The blood count was: haemoglobin, 13·4 g.; colour index, 0·99; red blood cells, 4,340,000; white blood cells, 7,900 per 100 c.mm. of blood; polymorphs, 51 per cent.; monocytes, 4 per cent.; lymphocytes, 43 per cent.; eosinophils, 2 per cent.

The sedimentation rate was: 15 mm. in the first hour. The blood Wassermann reaction was negative. The specific gravity of the urine was 1024, and there was no albumin or sugar. The Mantoux (1/1000) test was negative.

The glucose tolerance test was: fasting, 95 mg. per cent.; after ingestion of glucose, 70 mg., 80 mg., 90 mg., 50 mg. at half-hourly intervals. This represents doubtful increase of tolerance to glucose.

A radiograph of the wrist joint showed a normal ossification index.

Cerebrospinal fluid pressure was 110 mm. with no block (one lymphocyte; no bacteria; protein 70 mg. per cent.; chlorides 720 mg. per cent.; sugar 60 mg. per cent.; Wassermann reaction negative).

Eight hours after lumbar puncture the child complained of severe pain in the back and right hip which radiated down the back of the right leg. The pain persisted for two days. It then ceased but was replaced by an attack of headache and vomiting which lasted a further three days. The

post lumbar puncture episode was undoubtedly of some significance even though cerebrospinal fluid pressure was normal.

RADIOGRAPHY OF THE SKULL. The lateral radiograph of the sella turcica and the region of the sulcus chiasmaticus (Plate VIIa) revealed a characteristic enlargement of the anterior part of the sella turcica with an excavation of the under surfaces of both anterior clinoid processes. These changes were caused by a pressure atrophy, and the bone in the affected region was thinned. A lateral tomograph (Plate VIIb) of the sella turcica demonstrated these changes even more clearly.

Rhese Goalwin view (Plates VIIc and d) revealed an increase in the size of both optic foramina, the right more than the left. It is interesting to note that on the left side, the less affected side, the margin of the optic foramen was sclerosed, suggesting that in the early stages irritation may lead to sclerosis whilst later pressure causes atrophy of the foraminal margin.

An electroencephalogram with monopolar leads from both hemispheres showed rather erratic recordings. Mixed frequencies of 1-10 per second were present. It was concluded that there was cortical dysrhythmia without focalization; there was no evidence of epilepsy.

Consideration of the clinical findings pointed to a space-occupying lesion in the region of the pituitary fossa. The radiographs more accurately localized the lesion to the region of the sulcus chiasmaticus of the sphenoid bone and demonstrated that the floor and the posterior clinoid processes of the sella turcica were intact. In addition, there was enlargement of both optic foramina, indicating that both optic nerves were involved. A diagnosis of chiasmal glioma was made and an exploratory operation was advised to verify the diagnosis. Prefrontal craniotomy was undertaken by Dr. R. Krynauw, who reported: 'After the optic nerve had been stripped, a large pink tumefaction about the size of a pigeon's egg was encountered. It was continuous with the chiasma and extended backwards along the optic tracts. Removal of this lesion would be technically impossible or nearly so.' Three months after the operation the general condition of the child was unchanged. The right eye was totally blind.

Comment

Chiasmal glioma is essentially a condition of childhood. It arises in the chiasma or adjacent wall of the third ventricle, spreading forwards to involve the nerve even as far as the papilla. Intracranial involvement of the optic nerve is much rarer than intraorbital involvement. The growth is slow and may not cause death for many years. Davis (1940), reviewing the literature since 1876, found thirty-eight cases associated with neurofibromatosis, in twelve of which there was an hereditary element. Vision is involved early, and marked deterioration or even blindness may be present before symptoms of cranial hypertension manifest themselves. Visual affect is bizarre, optic atrophy and central scotoma tending to appear rather than bi-temporal or homonymous hemianopia. Where the nerve head has been invaded, exophthalmos may be present. In many of the reported cases endocrine symptoms have been absent, though Ford states that polydipsia, polyuria and obesity, consequent on pressure on the hypothalamus, are common. The radiograph shows a bulging or erosion beneath the anterior clinoids; enlargement of the optic foramina can often be observed.

Differential diagnosis. Other conditions involving the optic chiasma require consideration in the diagnosis, namely craniopharyngioma, pituitary tumour, aneurysm of the circle of Willis, suprasellar meningioma, and chiasmal arachnoiditis with cyst formation.

CRANIOPHARYNGIOMA. This is a not infrequent tumour of childhood, constituting roughly one-seventh of all intracranial neoplasms at this age, and is the most important condition requiring differentiation. The subject has been well reviewed by Ingraham and Scott (1946), who point out that, in contradistinction to chiasmal glioma, signs of intracranial hypertension such as headache and vomiting precede visual disturbance. The latter takes the form of lower quadrantic defects proceeding to bi-temporal hemianopia. Optic atrophy may occur. Evidence of acute hydrocephalus can be established by ventriculography. Pressure on the hypophysis commonly leads to arrested skeletal development, whilst hypothalamic signs are rare. In the radiograph suprasellar or intrasellar calcification is present in 75 per cent. of cases. Separation of sutures, convolutional atrophy, erosion of posterior clinoids, enlargement and distortion of the floor of the sella may also be noted in the radiograph. Pressure atrophy of the anterior clinoid processes is seldom marked, and when marked generally involves the superior surface of the anterior clinoid process in contradistinction to the chiasmal glioma (Plate VIIe).

PITUITARY NEOPLASM. The age factor operates heavily against a diagnosis of pituitary neoplasm, which is practically unknown under the age of ten years. Here, endocrine disturbance is to the forefront. Reference has already been made to the radiological location of the maximal pressure changes in chiasmal glioma as affecting the anterior part of the sella turcica with little involvement of the floor or post-clinoid processes. A pituitary tumour throws the main stress of pressure atrophy on the floor and post-clinoid process (Plate VIIf). A radiological appearance of an eroded anterior clinoid process without involvement of the floor or post-clinoid process is against the diagnosis of a primary pituitary neoplasm.

MENINGIOMA. The age factor applies similarly to meningioma, commonly seen in middle-aged adults. Meningioma arising near the body and lesser wing of the sphenoid generally produces some

sclerosis of the adjoining bone, and atrophy is less common.

ANEURYSM. This, too is not common in children. Associated palsies of third, fourth, and sixth cranial nerves may be present in addition to the chiasmal syndrome. Calcification may be detected by radiograph in the wall of the aneurysm, and the clinoids may show localized erosion. Angiography is conclusive.

ARACHNOIDITIS. This is usually the sequal of trauma and is unaccompanied by endocrine disturbance. Plain radiography is negative but encephalographic studies have shown characteristic appearances.

Summary

A case of chiasmal glioma is described and the clinical and radiological features discussed. A chiasmal syndrome in the first decade of life, with the radiological features of enlargement of both optic foramina, erosion beneath the anterior clinoid processes, and enlargement of the sulcus chiasmaticus is almost diagnostic of this condition.

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(For illustrations to this article see Plate VII, p. 259.)

HEREDITARY PHALANGEAL AGENESIS SHOWING DOMINANT MENDELIAN CHARACTERISTICS

BY

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AND

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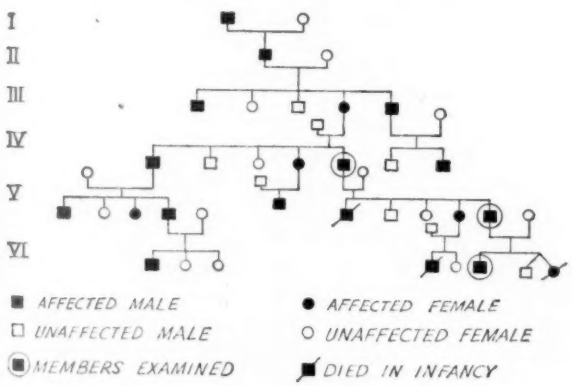
A healthy baby, six months old, was brought to the Duchess of York Hospital, Manchester, in July, 1946, suffering from phimosis. It was noticed that his hands were deformed. His mother, formerly a nurse, was herself normal, but stated that the child's father and grandfather and several other relatives were similarly affected. She was, therefore, asked to collect further information, from which the accompanying genealogical tree was compiled.



The deformity, an unusual one, was shown by radiograph to consist of absence of all the terminal phalanges of the fingers and also of the middle phalanges of the third and fourth fingers. In the first and second fingers the middle phalanges were rudimentary, and this was more marked in the right than in the left hand. The terminal phalanx of the left thumb was bifid, that on the right partially bifid.

The deformity of the fingers appears to be almost the same in all affected members of the family, the distal phalanges being absent and the middle phalanges either absent or rudimentary, but there is some variation in that of the thumb. For instance, the patient's right thumb is partially bifid like those of his grandfather, his left completely bifid like those of his father. There has been deformity of the toes in all the affected members except the patient's, where only a slight webbing is present. The grandfather's foot deformity consists in absence of the distal phalanx of the third and fourth toes. It causes no difficulty in walking. Radiographs of the child's and the grandfather's hands and feet are shown (Plate VIII). The father, unfortunately, was unable to attend for x-ray examination, but has been examined by one of us (N. H. W.) and found to be similar to the grandfather with the exception of the thumbs which are splayed, suggesting the presence of a bifid terminal phalanx comparable to that in the child's left thumb.

In July, 1947, the mother again attended the out-patients' department, this time with a normal male child aged nine weeks. This child was the first-born of dissimilar twins and weighed 3 lb. at birth. The second twin, a girl weighing 4 lb. 10 oz., was reported to have shown the same phalangeal agenesis as the rest of the affected members of the family. Unhappily she died within two days of birth. We are indebted to the resident obstetric surgeon of St. Mary's Hospital, Manchester, for the following report on the female twin: 'There was complete absence of the terminal phalanges of both hands with splaying of the thumbs. The toes were normal.' There is a history of twins in the mother's family, but none in the father's.

The mother was sure that no case had occurred in the children of unaffected members of the family. Their offspring are therefore not included, and no details are available of the siblings of the first and second generations. The offspring of some of the distant members of the family are not known, but, where given, they are complete.

It was stated that all the affected members were musical and had 'wonderful singing voices.' The family as a whole enjoyed music, but the affected members could 'sing and play easily and earn their living by it,' whereas the others could not. This statement was not confirmed for all the affected members, but in the immediate family of the child examined the great-grandfather was a church organist, and the grandfather was a singer on the variety stage. The father is by trade a cooper, but we are told he has an excellent singing voice.

The condition has been handed down from parent to child for six generations. In the complete families of the third to the sixth generations there are thirty children, of whom eighteen are affected. Of the affected members, thirteen are males and five are females. In all the families but one, the first child is an affected male followed by an unaffected child, even in the twins.

The condition would therefore appear to be a heterozygous dominant. There have been no cousin marriages to illustrate the homozygous effect. The degree to which individual members are affected varies. In all but the patient and his sister, both hands and feet are deformed. In some the thumbs are merely flattened, in others definitely splayed.

No other deformity was discovered in the child, father, or grandfather examined. The family as a whole is reported to be healthy and many members have lived to over seventy.

Discussion

The mating of a dominant heterozygous individual with a recessive homozygote produces a back cross generation of equal numbers similar to the parents. The expected ratio of unaffected to affected members would therefore be 1:1. In the case under discussion, it is twelve unaffected to eighteen affected, in the siblings of the complete families. Of the latter, thirteen are males and five females.

There is no evidence of complete sex linkage. The preponderance of males is not so great as at first appears, as the total number of males is high, being 19:11. The deformity is therefore carried by a dominant autosomal gene.

The marked musical capacity of the affected members suggests that there is a linkage between the gene producing the developmental defect and one influencing voice production and musical capability.

Summary

A description is given of an inherited deformity of the extremities showing a combination of ectrodactyly and polydactyly passing through six generations as a heterozygous dominant with some male preponderance. The gene appears to be linked with one producing musical capability.

(For illustrations to this article see Plate VIII, p. 260.)

ACUTE BACTERIAL ENDOCARDITIS WITH A POSITIVE BLOOD CULTURE IN A CHILD AGED ONE YEAR

BY

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Cases of acute bacterial endocarditis in infancy are reported from time to time. Sansby and Larson (1930) give a review of the literature and report a case in an infant of five weeks old. MacGregor and McKendry (1944) report a case of foetal endocarditis, the infant being cyanotic through its fifteen days of life. The valve cusps showed nodular thickenings and other signs of inflammatory changes. Dean (1912) reports a case due to the pneumococcus in a child of three years in which both mitral and tricuspid valves were affected, and he comments on the fact that the valves on the right side of the heart were involved. The pneumococcus was found in the cerebrospinal fluid before death, in the heart blood before the heart was opened, and in films made from the surface of the brain. There was no pneumonia.

Endocarditis in infancy is most likely to be caused by the streptococcus, especially if a massive dose results from an acute throat infection. Endocarditis resulting from chronic tonsillitis and repeated infections, such as those met with in rheumatism, is not usually seen in infancy though it is at a later age. Holt and McIntosh report that in a thousand autopsies they found no case of endocarditis under three years old.

Brandes (1933) reports a case of gonococcal endocarditis of the tricuspid valve in an infant of ten days suffering from gonorrheal conjunctivitis. The child had a patent ductus arteriosus which may have contributed to the endocarditis. Kehr and Adelman (1942) report a case due to a haemolytic streptococcus, and Sanders (1933-4) a case associated with pyodermic infection. Wolff (1940) records two cases in infants diagnosed during life and treated as out patients and cured after severe illnesses: one of them had a purulent pericarditis. Both cases were staphylococcal in origin, from furuncles at the back of the head. These cases were treated by blood intravenously, and intramuscularly by small doses of prontosil and vitamin C. Recovery was apparently complete.

Clinical Aspects

In Sansby and Larson's (1930) case there was a sudden onset with fever, rapid loss of weight, frequent stools, and a dulled sensorium suggesting a toxicosis. Treatment had no effect. No murmur was detectable in the heart and only an autopsy explained the rapid progress of the illness.

Case History

Our case showed the following history and clinical features and pathological findings.

S. H., a female, aged one year and one month, admitted on April 25, 1946, died on May 8, 1946. Delivery had been normal. The history was uneventful until the age of three months, when she had attacks of lethargy. In these she was ill and lifeless and feverish for about ten days. The first attack was diagnosed as bronchitis, the second as gastro-enteritis. With these attacks the ears discharged. In September, 1945, she was admitted to Booth Hall Hospital with severe gastro-enteritis and dehydration, and she had a transfusion. Dr. Patterson, Medical Superintendent, reports that there were no cardiac murmurs when she was discharged.

On examination on April 25, 1946, there was a mucoid discharge from the right ear, a loud systolic murmur all over the praecordium, and tachycardia; a diagnosis of endocarditis was made. The murmur did not suggest pericarditis. Dullness was present over the left side of the chest below the apex, with harsh breathing in the left axilla; the abdomen was a little tumid and the spleen palpable, but not readily so.

The child improved at first and tried to play in her cot, but she was still pale and the murmur had not diminished.

On April 25 a radiograph of the heart shadow showed only slight general enlargement, globular and suggestive of pericarditis. Some hilar thickening was present. A blood count showed 54 per cent. haemoglobin, 3,500,000 red cells and 6,800 white cells per ml. of blood, polymorphs 57 per cent. A blood culture showed a profuse growth of pneumococci. Sulphaguanidine and penicillin, 10,000 units three-hourly, were given, and later

sulphamezathine. An oxygen tent was used. On May 2, the heart sounds were free from murmur and blood culture negative, but the blood count showed 45 per cent. haemoglobin and 4,230,000 red cells per ml. of blood.

On May 8 the child became worse, and developed dyspnoea, extreme pallor, bronchial breathing, and râles suggesting terminal pneumonia. She died at 10 p.m. The temperature throughout showed only occasional rises up to 100° F. The pulse was very rapid, between 130 and 170 per minute. The respirations were slightly raised.

Post-mortem findings. There was slight wasting of the subcutaneous tissues. The heart (80 g.) was increased in weight for the age by about one-third. This was mainly due to hypertrophy of the left ventricle (see illustration, Plate VII). A large vegetation was present on the anterior curtain of the mitral valve (1 cm. broad by 0·7 cm. deep) and extending on to the chordae; a much smaller vegetation was present on the posterior curtain. There was no thickening of the cusps. Microscopically the large vegetation was found to consist mostly of thrombus which in some places was undergoing organization, whilst in other places there were groups of organisms surrounded by polymorphic leucocytes. The organisms were in pairs, gram positive, and lanceolate ovoid in shape. Polymorphs were also present in the valve cusp at the base of the vegetation, but the remainder of the valve appeared normal. The other valves were normal. Between the lobes of the lungs were fine adhesions. Above the bronchi at the hilum of each lung was a mass of glands (2 to 2·5 c.mm. in diameter). The outer surfaces of the lungs were dark red, but there were a few lighter pink patches which tended to be raised. The cut surface showed a similar appearance, i.e. mainly dark red with smaller pink patches scattered throughout. The lungs were indurated throughout the greater part. Microscopically, many of the alveoli were filled with macrophage cells (large cells with pale nuclei and abundant slightly eosinophilic cytoplasm); some also contained a little fibrin and other polymorphs. Relatively few alveoli were aerated. Some of the alveolar walls tended to be thick due to the large numbers of mononuclear cells in them; others were congested. A moderate number of bronchioles contained polymorphs and some macrophage cells, and were surrounded by a loose zone of lymphocytes which extended into the inter-lobula septa. The appearances were those of early resolution. Both mastoids were healthy; a little greenish mucoid material was present in both middle ears. The brain was slightly congested. The mesenteric lymph nodes were slightly enlarged. The spleen (40 g.) was nearly twice its normal weight; the Malpighian bodies were well defined. The other organs showed no significant abnormality.

Comment

The appearances were those of bacterial endocarditis of the mitral valve and resolving bronchopneumonia with marked macrophage reaction. The immediate cause of the left ventricular hypertrophy was not obvious.

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(For illustrations to this article see Plate VI, p. 258.)

REVIEWS

A Way of Life for the Handicapped Child. By EIRENE COLLIS, M.C.S.P., M.A.O.T. 1947. London: Faber and Faber. Pp. 183. (Price 10*s.* 6*d.*)

The handicaps to which the title refers are those produced by cerebral palsy. Mrs. Collis studied them under W. M. Phelps at the Children's Rehabilitation Institute at Cockeysville, Maryland, in 1941. She has been chief therapist at the L.C.C.'s Cerebral Palsy Unit since its inception in 1943. In her conception of the disease and in the physiotherapy she employs she follows Phelps's teaching, but unlike him she makes little or no use of splints or drugs.

Treatment is based on certain theories of muscular action:

From the point of view of movement cerebral palsies may be divided into five types, of which two are common: the spastic and the athetoid.

Volitional movement is initiated by the cortex, which controls contraction and relaxation of the muscle acting as prime mover. Contraction and relaxations of synergists, antagonists, fixators, etc., are laid down as an invariable action pattern in subcortical centres, ready to be activated by the cortical impulse.

In spastic paresis the cortex is involved and many prime movers, particularly those put in tension

by gravity, have hyperactive stretch reflexes. For example, in the standing position biceps is the prime mover for extension and flexion of the elbow. If the muscle is spastic, extension is limited by stretch reflexes. If the arm is placed above the head, or if the child is held upside down, triceps becomes the prime mover. It is usually not spastic, and flexion and extension of the elbow become easy. If the action of gravity on the limb is abolished, or reversed by position, the child can in time be taught to control biceps. This explanation is perhaps oversimplified, but it is by analysing the functional defect, and by designing special exercises to overcome each particular disability, that the therapist educates the spastic child in movement.

In athetosis volitional movements are initiated normally. They are not carried out normally because subcortical defects interfere with the action patterns of antagonists, etc., and produce inchoate movements. These may be inhibited by voluntary, later habitual, muscular spasm. Both spasm and movements disappear during sleep, and children can be trained to make them disappear by voluntary relaxation. When they have mastered this they can be taught new action patterns under the control of the undamaged cortex. This involves the conscious use of synergists, etc. Here again observation, analysis, planning, and meticulous attention to detail are needed.

The principles and practice of these methods are described in this book, along with much else that concerns the child with cerebral palsy. The paediatrician will find here things for pondering and for criticism. Even if he disagrees with some of the theory he will find a great deal of useful practical information. This is an important book in a neglected field.

The volume is attractive in appearance, the price is reasonable, the bibliography is bad, the illustrations of equipment good. The author has read widely and thought deeply about her subject. Neither it nor her literary constructions are always easy to understand, but the effort should be made.

Advances in Pediatrics. Vol. 2. Edited by S. Z. LEVINE, A. M. BUTLER, L. EMMETT HOLT, Jr., and A. ASHLEY WEECH. Pp. 407. (Price 40*s*. 6*d*.)

Advances in Internal Medicine. Vol. 2. Edited by W. DOCK and I. SNAPPER. Pp. 642. (Price 57*s*.) 1947. Interscience Publishers, New York and London.

These two volumes both set a high standard of scholarship and contain a series of original reviews by authors well qualified to write on their particular subjects. The first includes discussions on the etiology of congenital malformations (J. Warkany); acute infectious lymphocytosis (C. H. Smith); the rôle of fluorine in prevention and treatment of dental caries (H. T. Dean); the treatment of purulent meningitides (H. E. Alexander); chemotherapy: penicillin, sulphonamides, streptomycin, and tyrothricin (P. György and H. F. Lee); atypical pneumonia (J. H. Dingle); endocrine and other factors determining the growth of children (N. B. Talbot and E. H. Sobel); virus diarrhoea (K. Dodd); prematurity (H. H. Gordon); the genesis of physiologic hyperbilirubinaemia (A. A. Weech); and the prevention of recurrences of rheumatic fever (A. G. Kuttner).

Advances in Internal Medicine includes several sections of interest to the paediatrician, for example, the problem of the Rhesus antigen in medicine (A. S. Wiener); nutritional requirements in disease (C. M. MacBryde and R. Elman); and a discussion of angiocardiography and angiography (M. L. Sussman and A. Grishman). Three British authors are included, J. McMichael contributing a section on circulatory failure studied by means of venous catheterization, L. S. P. Davidson on pernicious anaemia, and L. J. Davis on megaloblastic anaemias.

Both volumes are well illustrated and produced, and each section is admirably supplied with references.

Psychiatric Interviews with Children. Editor: HELEN LELAND WITMER. 1947. New York: The Commonwealth Fund, London : Geoffrey Cumberlege. Pp. 443. (Price $4·50 or 25s. 6d.)

This valuable book is written in clear English and divided into three parts.

The author has examined one or two cases as reported from each of eight American child guidance clinics, and she has used the material to formulate common denominators, a task which proves to be practicable in spite of the distinct types of approach employed in the various clinics and in spite of the fact that distinct schools of thought are involved.

The first and last parts of the book can be read quickly enough and with profit by any one familiar with psychotherapy of children. The middle section (380 pages) demands hard work from the reader and sacrifice of time, as clinical reports of psychiatric work must always do.

In Part I three subjects are studied. (1) What is the nature of child guidance? (2) What kind of children attend these clinics? and (3) In what way are changes brought about? (The dynamic of therapy: 'It is through the use of words—and actions that are equally symbolic—that psychotherapy is carried on. Their value to the child (both his own words and actions and those of the therapist), however, derives from the therapeutic relationship. It, therefore, is the underlying dynamic and upon its proper use most of therapy depends "—p. 48.)

Part II consists of detailed and honestly reported case-work, well worth study both individually and comparatively. In Part III the editor makes comments. After a review of the cases she concludes: 'Treatment method, then, grew out of both general theoretical consideration and the specific nature of the patient's problem; consequently it varied considerably from case to case.'

Finally Witmer states that her aim has been: '. . . to show that psychotherapy is a living process, not a text book of set rules, and that he who would practise it must learn how to translate theory back into the language from which it originated—the symbols that two persons, psychiatrist and patient, use when they want to communicate with each other to therapeutic ends ' (p. 433.)

The most topical page (in view of the recent publication in England of Anna Freud's book, *The Psycho-Analysis of Children*, is that on which there is a discussion of the establishment of the therapeutic relationship (p. 39): ' Anna Freud says that the psychiatrist must strive to secure from the child an affectionate attachment, with its accompanying faith in the therapist, admission of illness, and desire for recovery. To this end she suggests that the therapist strive for the child's love, stress the seriousness of his disability, and insinuate himself into his confidence.

' American child psychiatrists (perhaps reflecting American belief in individualism, even for young children) put less emphasis on " winning " the child and more on the child's own interest in being helped.'

Many British child-analysts would range themselves with Witmer in this discussion, if the description of Anna Freud's view is accurate. British child-analysts might go further and express doubt as to whether even Witmer and her co-authors have appreciated the full depth of the unconscious co-operation of the child in a working analysis.

Mongolism and Cretinism; A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency. By CLEMENS E. BENDA, M.D., Director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Mass. 1947. London: William Heinemann (Medical Books), Ltd. Pp. 330. (Price 25*s*.)

This book is based on a study of over three hundred cases of mongolism and fifty autopsies, a number of the cases having been studied over a period of ten years. Cretinism has been included for purposes of comparison and contrast, though it is treated less fully. The most interesting section is that dealing with endocrine pathology in both conditions. In forty-eight autopsies on mongols, the author considered the thyroid normal in only two, whilst the anterior pituitary he describes as showing two types of pathology: (1) deficiency of the gamma cell system and general inability of formation of chromophilic elements, and (2) chromophilic shift toward eosinophily with absence or deficiency of gamma cells and pathology of beta cells. He considers mongolism an example of primary pituitary dysfunction and that therapy calls for the use of an effective anterior pituitary extract. Such he admits is not yet available, but he claims some effect with a thyrotropic hormone used in a single case after thyroid administration alone had proved ineffective. He urges more detailed endocrine studies during pregnancy with a view to determining latent hypothyroidism, hypopituitarism, or hypogonadism, and adopts a somewhat optimistic view with regard to the future possibilities of preventing mongolism. The book is well worth reading if only because the author is not prepared to accept the completely defeatist attitude toward one of the commonest types of mental defect. The fact that the reader is unlikely to go all the way with him, even in his description of the mongol as a ' pituitary cretin ', does not lessen the book's interest.

Diseases of Children's Eyes. By JAMES HAMILTON DOGGART, M.A., M.D., F.R.C.S., Ophthalmic Surgeon, Hospital for Sick Children, Great Ormond Street, and St. George's Hospital, London. With 210 illustrations including 32 coloured plates. 1947. London: Henry Kimpton. (Price 42*s*.)

The author has performed a real service to the profession in bringing together in one volume of reasonable compass the widely-scattered information on which it is based. The physiology and anatomy of the eye in infancy and childhood is seldom well described even in the larger works of reference devoted primarily to diseases of the eye in adult life, whilst it is often necessary to hunt the literature for information on diseases peculiar to childhood which may have secondary ocular manifestations. Minor criticisms might be made: a rather high proportion of the illustrations are borrowed from other authors, and the references are not as extensive as might be desired; the sections on disordered movement and squint, though excellent, might well have been expanded in view of the importance of these conditions. In general, however, this is a thoughtful, stimulating book based both on wide personal experience and reading, and one which should prove invaluable for reference to both the ophthalmic surgeon and the paediatrician.

A Study of Individual Children's Diets. By E. M. WIDDOWSON. Medical Research Council Special Report Series No. 257. 1947. London : H.M. Stationery Office. (Price 6*s*.)

This is a study of the individual diets of one thousand children, carried out from 1936 to 1939. The food eaten by each child was weighed over a period of one week, and the diets translated into terms of their constituents. The diets were correlated with individual heights and weights, and some other clinical observations were made. It is regrettable that the long delay in publication has rendered some of the data of historical interest only; but it will at least serve as a valuable standard for comparing with conditions in later and less happy days.

Office Immunology. Edited by MARION B. SULZBERGER and RUDOLF L. BAER. 1947. Chicago. The Year Book Publishers, Inc. Pp. 420. (Price, 36*s*.)

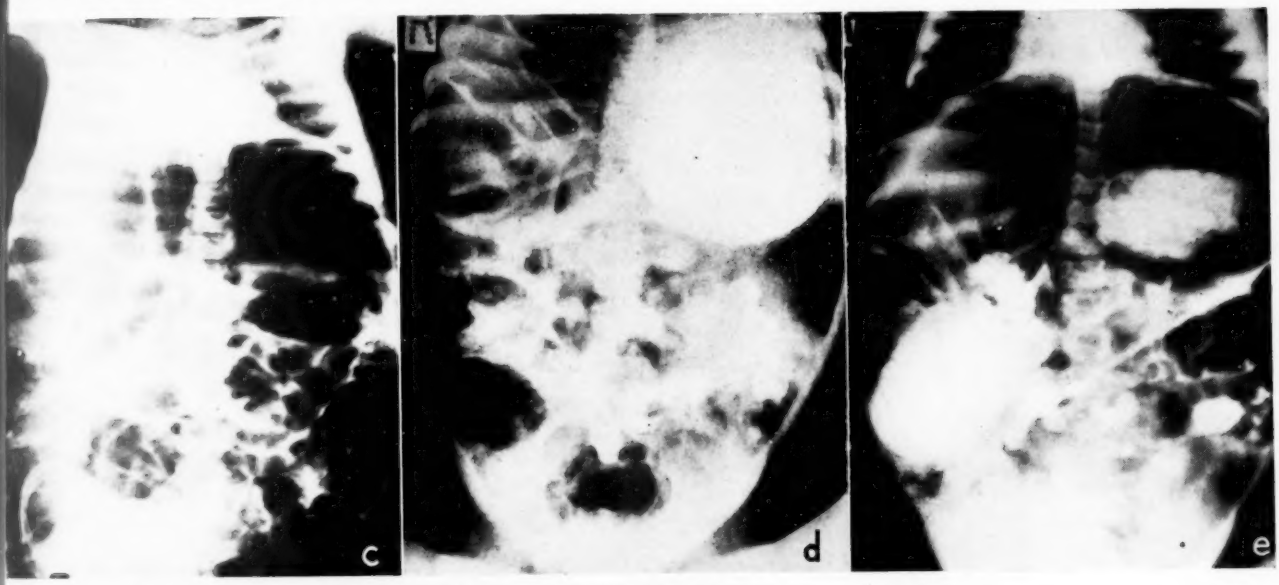
(a)—The older twin (A) showing gross abdominal distension, with wasting of the rest of the body. Note the marked gluteal wasting.

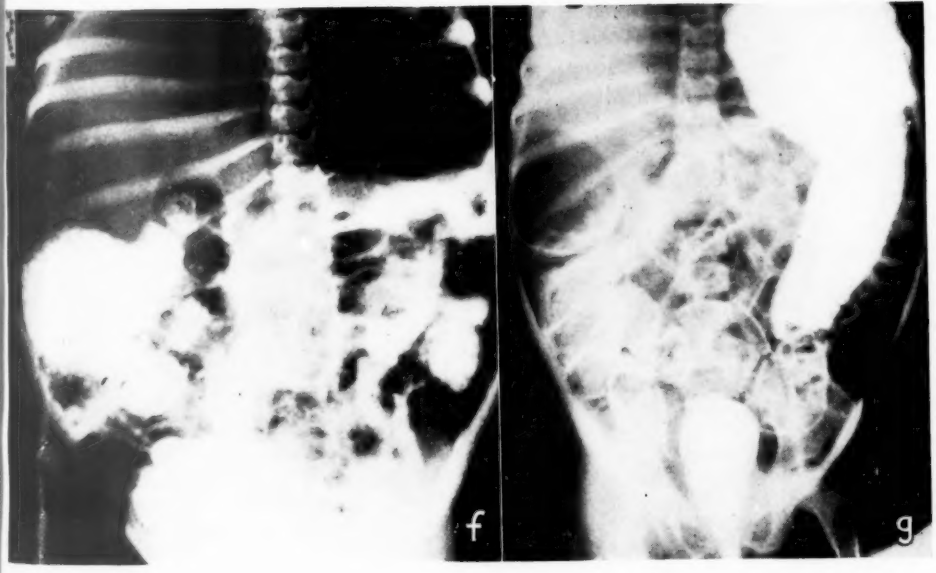
(b)—The younger twin (B) showing gross abdominal distension, but with less marked general wasting than in A.

(c)—Radiograph of A showing upward displacement of heart shadow, and of lungs.

(d)—Radiograph of A two hours after barium meal. It shows tremendous dilatation of the stomach.

(e)—Radiograph of A four hours after barium meal, showing 2 loculi in the greatly distended stomach.

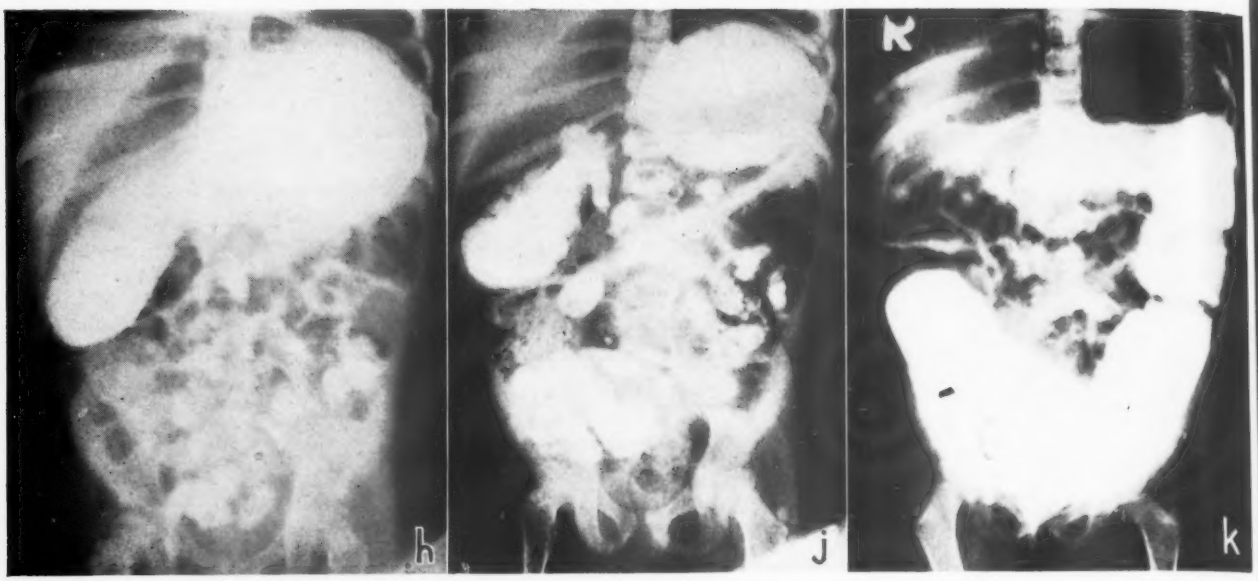




(f)—Radiograph of A five and a half hours after barium meal, showing almost empty stomach with considerable distortion in the position of the pyloric outlet and duodenal bulb.

(g)—Radiograph of A after barium enema, showing redundancy and dilatation of the descending colon.

PLATE V



h.—Radiograph of B half an hour after barium meal, showing biloculation of the stomach and gross dilatation. j.—Radiograph of B showing distortion of pyloric outlet and duodenal bulb. k.—Radiograph of B showing marked redundancy and dilatation of colon as far as the splenic flexure.

ACUTE BACTERIAL ENDOCARDITIS BY LAPAGE AND LANGLEY

(l)—Heart, showing hypertrophy of left ventricle, and vegetation on anterior curtain of mitral valve.

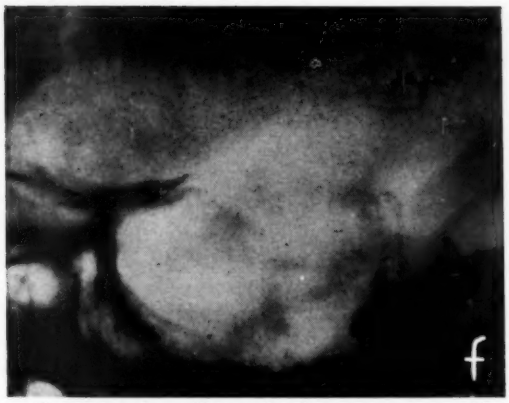
PLATE VI

(a)—Lateral localized view of sella turcica ; shows excavation beneath anterior clinoid processes and pressure atrophy of floor of sulcus chiasmaticus. The sella turcica behind this area is unaffected.

(b)—Tomographic film taken at 5 c.m. in the lateral position. The changes in the bony walls of the sulcus chiasmaticus can be clearly seen.

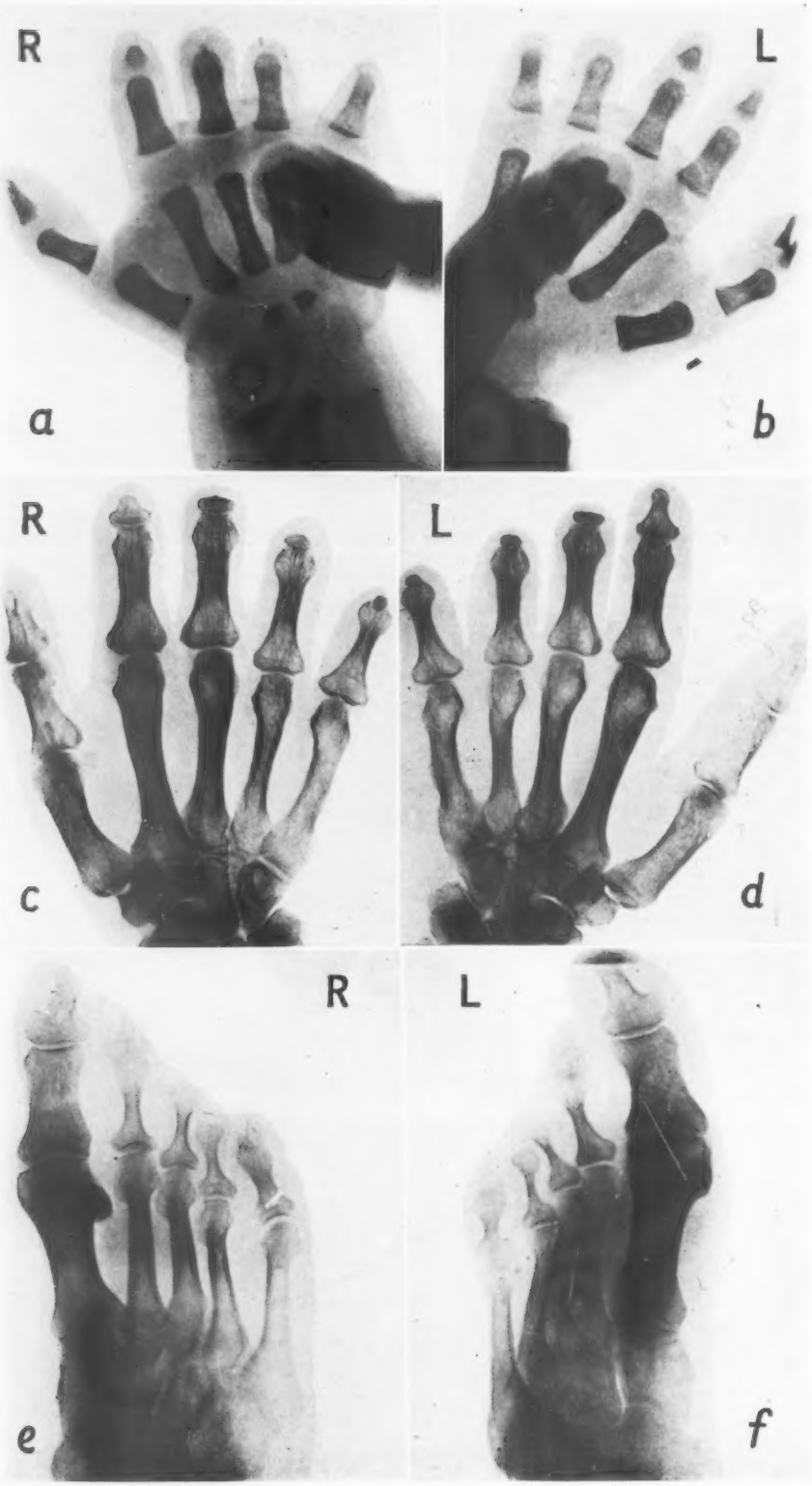
Rhese Goalwin view of (c) left optic foramen, to demonstrate enlargement of optic foramen ; and (d) right optic foramen, to show massive enlargement of that structure with thinning of surrounding bony wall.

(e)—Lateral radiograph in a case of craniopharyngioma, for comparison. Note erosion of upper surface of anterior clinoid processes, and the calcification.



(f)—Lateral radiograph from a case of a chromaphobe adenoma of the pituitary. Note generalized enlargement of pituitary fossa, and especially the manner in which the main stress falls on the posterior clinoid processes.

PLATE VII



Shows (a) baby's right hand, (b) baby's left hand, (c) grandfather's right hand, (d) grandfather's left hand, (e) grandfather's right foot, and (f) grandfather's left foot.

PLATE VIII

Infant Feeding—

The Logical Approach

Nature has provided for the human infant a milk of specific composition and having clearly defined characteristics.

Consequently, it is logical to conclude that a satisfactory substitute for human milk should conform as closely as possible to the nutritional standard of breast milk.

It is this rational principle which governs the manufacture of Humanised Trufood.

	HUMAN MILK	HUMANISED TRUFOOD
Protein	1.3	1.6
Fat	3.4	3.4
Lactose	6.9	6.5

PROTEIN The composition of the protein of Humanised Trufood is adjusted to approximately an equal ratio of casein and soluble protein.

FAT The fat is presented in the form of a finely diffused emulsion.

LACTOSE Lactose is the only carbohydrate present and forms 50/55% of the total solids.

DEHYDRATION The Powder is produced by the spray process and on reconstitution with water, presents the closest possible approximation to human milk.

1 OZ. OF POWDER PROVIDES:—

0.3 mg. Iron — 600 I.U. Vitamin A
150 mg. Calcium — 320 I.U. Vitamin D
150 mg. Phosphorus
146 Calories

Enquiries to be addressed to:—

TRUFOOD LIMITED, (Dept. ADC4),
BEBINGTON, WIRRAL, CHESHIRE

TF 302/23

TRUFOOD PRODUCTS OF REPUTE

Sunday Morning 1887

It is the year of the Golden Jubilee. Miners are earning 36/- a week and everyone is talking about Stevenson's new novel "Dr. Jekyll and Mr. Hyde." The boy in the bassinette is six months old. His mother is giving him M.O.F. —"one of those new-fangled foods."

Scott's of Edinburgh launched M.O.F. in the '80's. Then it was confined to Scotland. It was not until 1941 that Scott's made M.O.F. available throughout the whole of England. In the '80's it was a very modern food. It still is. M.O.F. has kept in step with the progress of nutritional science. Today it is fortified with iron, calcium, phosphorus and vitamin D — in keeping with the current trend in infant nutrition. Even though M.O.F. was not distributed on a national scale until 1941, now more than half of the country's infant welfare centres are recommending it.

And what is equally important, the grandchildren of the boy in the bassinette like their M.O.F.

Scott's of Edinburgh are naturally proud of the success that M.O.F. has achieved. They are planning other infant foods which they are confident will achieve the same measure of acceptance.

SCOTT'S OF EDINBURGH

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